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Development of Novel Isocyanide Based Multicomponent Reactions

A thesis submitted in partial fulfilment of the requirements for the award of the
degree of

DOCTOR OF PHILOSOPHY

At the Chemistry Department of University College London

by

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September 2008

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Robert William Waller

September 2008

To Aurora

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To Aurora, I am forever indebted to you for all of the love and support you have given me during my write-up, I hope that I can repay you in the years to come.

Lastly, but by no means least, thank you to all of my family for their support during my education.

Abstract.

This thesis is divided into three parts. Part one presents an overview of isocyanide based multicomponent reactions, with a particular emphasis placed upon bifunctional substrates and novel nucleophilic partners for the Ugi reaction.

Part two discusses the development of three-component reactions between *N*-alkyloxazolidines, isocyanides and carboxylic acids. This reaction is then further developed to allow it to be carried out in a four-component manner from an aminoethanol and carbonyl compound rather than an *N*-alkyloxazolidine. The use of *NH*-oxazolidines in a surprising three-component reaction with isocyanides and carboxylic acids is then discussed, with interesting mechanistic consequences. Novel nucleophilic partners for reactions with oxazolidines and isocyanides, rather than the ubiquitous carboxylic acids are then discussed, giving rise to novel structural frameworks.

Bifunctional carbonyl-carboxylic acid substrates are then investigated as substrates for isocyanide based multicomponent reactions involving ethanolamines, leading to exciting new medium sized ring systems.

Finally, hydroxy-carbonyl compounds are briefly discussed as substrates for isocyanide based multicomponent reactions.

Part three describes the experimental procedures employed and results obtained.

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Abbreviations.

Δ	heat.
2-CR	2-component reaction.
3-CR	3-component reaction.
4-CR	4-component reaction.
A-4CR	Asinger four-component reaction.
Ac	acetatyl.
AcOH	acetic acid.
Ar	aromatic.
aq.	aqueous.
b	broad.
B	base.
br	broad.
Bn	benzyl.
b.p.	boiling point.
Bu	butyl.
Cbz	benzyloxycarbonyl.
CI	chemical ionisation.
CID	collision induced dissociation.
CH ₂ O	para-formaldehyde.
Cy	cyclohexyl.
d	doublet.
d.	day.
Da	Daltons.
DCM	dichloromethane.
<i>de</i>	diastereomeric excess.
DIPEA	diisopropylamine.
DMF	dimethylformamide.
DMSO	dimethylsulfoxide.
DoE	design of experiments.
E	energy.
<i>ee</i>	enantiomeric excess.
EI	electron impact ionisation.
El	electrophile.
ES	electrospray ionisation.
Et	ethyl.
eq	equivalent(s).
Et ₂ O	diethyl ether.
EtOAc	ethyl acetate.
EtOH	ethanol.
EWG	electron withdrawing group.
FAB (pos)	positive ion fast atom bombardment.
FTIR	Fourier transform infra-red.
h	hour.
HOMO	highest occupied molecular orbital.
HMBC	heteronuclear multiple-bond correlation.
HPLC	high performance liquid chromatography.
HRMS	high resolution mass spectrometry.
Hz.	Hertz.
IMCR	isocyanide based multicomponent reaction.
IPA	isopropanol.
IR	infra-red.
ⁱ Pr	<i>iso</i> -propyl.
J	coupling constant.

lit	literature.
LUMO	lowest unoccupied molecular orbital.
LRMS	low resolution mass spectrometry.
<i>m</i>	<i>meta</i> .
m	multiplet.
M	Molar concentration.
Me	methyl.
MeCN	acetonitrile.
MeOH	methanol.
MCR	multicomponent reaction.
min	minute(s).
Mmol	millimole.
mol.	Mole.
NMR	nuclear magnetic resonance.
nOe	nuclear Overhauser effect.
ⁿ Pr	<i>n</i> -propyl.
Nu	nucleophile.
<i>o</i>	<i>ortho</i> .
o.n.	overnight.
OVAT	one variable at a time.
<i>p</i>	<i>para</i> .
P-3C-2CR	Passerini, three centered, two-component reaction.
P-3CR	Passerini, three-component reaction.
Phth	phthalimido.
<i>p</i> TsOH	<i>para</i> -toluene sulfonic acid.
Ph	phenyl.
PS	proton sponge.
PRESS	sum of squares predicted error.
q	quartet.
qn	quintet.
R	any organic substituent.
RDS	residuals.
r.f.	retention factor.
r.t.	room temperature.
SSR	sum of squares regression.
SST	sum of squares total.
<i>t</i>	tertiary.
t	triplet.
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene.
^t Bu	<i>tertiary</i> -butyl.
TEA	triethylamine.
tert.	tertiary.
Tf or Triflate	trifluoromethanesulfonate.
TFA	trifluoroacetic acid.
TFE	trifluoroethanol.
TLC	thin layer chromatography.
Ts	toluenesulfonyl.
THF	tetrahydrofuran.
U-3CR	Ugi, three-component reaction.
U-4CR	Ugi, four-component reaction.
U-4C-3CR	Ugi, four centred, three-component reaction.
U-5C-4CR	Ugi, five centred, four-component reaction.
UV	ultraviolet.

Part 1:

INTRODUCTION

1.1 General Remarks.

This present thesis describes research into novel isocyanide based multicomponent reactions (IMCRs). In consequence, the introductory chapter firstly explains the basic concepts of a multicomponent reaction, briefly discussing some important examples. Isocyanides are then discussed as a framework for the subsequent overview of classical and contemporary isocyanide based multicomponent reactions. Due to the extremely large amount of work carried out in the field of IMCRs and the number of recent reviews in the area,¹⁻⁵ this introduction is not meant to be an exhaustive analysis of the field. Instead, particular emphasis is placed upon bifunctional substrates as well as novel nucleophilic partners for the Ugi reaction due to their later relevance to this work.

1.2 Multicomponent Reactions (MCRs).

A multicomponent reaction (MCR) may be loosely defined as a reaction involving three or more starting materials in which the majority of the atoms of each of the starting materials are incorporated into the final product. More than one of the functional groups may be present in any one starting material. In the ideal world, MCRs are ‘one-pot’ syntheses in which all of the starting materials are simultaneously present and react in sequential fashion in an ordered sequence according to a series of equilibria. MCRs may be divided into three types (Table 1).⁵

MCR Type	Reaction Scheme
I	$A + B \rightleftharpoons C \rightleftharpoons \dots N \rightleftharpoons \text{Product}$
II	$A + B \rightleftharpoons C \rightleftharpoons D \rightleftharpoons \dots N \rightarrow \text{Product}$
III	$A \rightarrow B + C \rightarrow D \rightarrow \dots N \rightarrow \text{Product}$

Table 1. Three basic classifications of MCRs.

Type I MCRs lead to varying yields, as the reaction will not reach preparative completion upon reaching equilibrium without employing methods to shift this equilibrium in favour of the products by Le Chatelier's principle. Type I MCRs are thus not considered to be preparatively useful, as complex mixtures are likely and side reactions often occur. On the other hand, type II MCRs are of much greater synthetic value, as the final irreversible step drives the overall reaction to completion, thus resulting in good yields and few side products. Most side reactions are, in this case, reversible. Type III MCRs are rarely seen *in vitro* but are often seen in biological processes as a result of quasi-irreversible partial reactions driven by thermodynamic factors and enzymatic catalysis.

1.21 The Advantages of Multicomponent Reactions (MCRs).

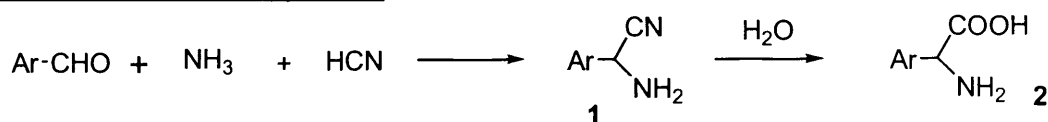
MCRs have many benefits over simple, conventional two-component reactions. In a stepwise iterative synthesis, the complexity and preparative difficulty increases in proportion to the number of steps, with subsequent purification and characterisation often required at each stage. This is both time consuming and also results in inherently poor yields over the many steps unless the alternative strategy of an extremely convergent synthesis is planned. MCRs reduce the need for so many isolation, purification and characterisation steps as well as the extended use of protection and deprotection protocols. This leads to increased productivity and vastly increased yields for complex targets. MCRs are also particularly adept for application towards diversity orientated synthesis, since at least three points of structural diversity may be achieved by the systematic use of structural variation of each of the starting materials during the multicomponent step of the synthetic scheme. Coupled with these benefits is the fact that most known MCRs use simple readily available starting materials with great atom efficiency,¹ thus reducing waste. In

essence, the ‘one pot’ nature of these reactions makes them both simple to carry out and ideal for automation.

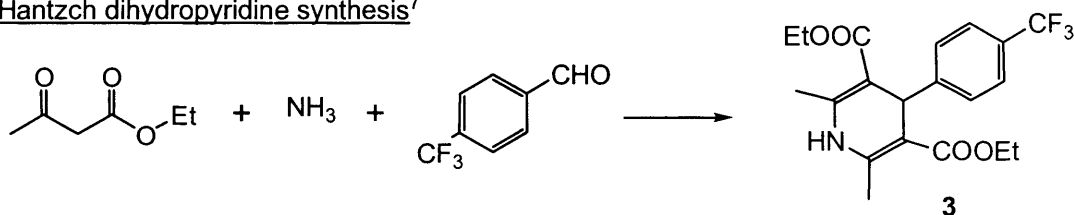
1.22 The History of the Multicomponent Reaction (MCR).

The Strecker synthesis of α -amino acids in 1850 is generally recognised as the first synthetically useful reported MCR (Scheme 1).⁶ Following this, a series of heterocycle forming MCRs were published over the next half a century all of which are still in common use today (Scheme 1).⁷⁻¹⁰

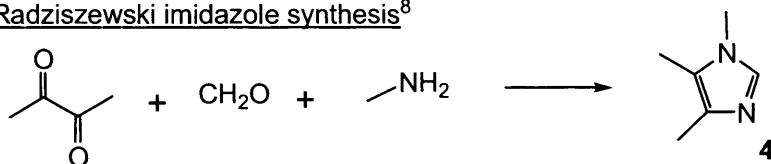
Strecker α -amino acid synthesis⁶



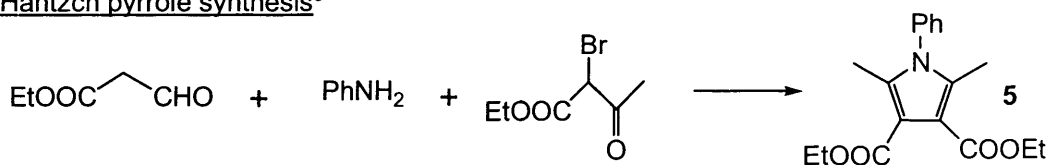
Hantzsch dihydropyridine synthesis⁷



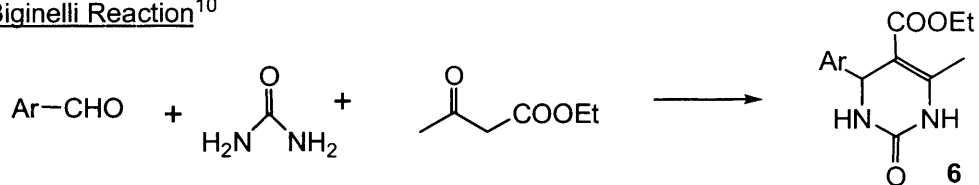
Radziszewski imidazole synthesis⁸



Hantzsch pyrrole synthesis⁹



Biginelli Reaction¹⁰



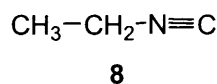
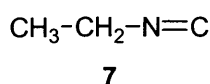
Scheme 1

Many of these early MCRs revolve around the important carbonyl and amine to imine functional group transformation.

In 1921, Passerini published the first reported isocyanide based three-component reaction (P-3CR) between an isocyanide, a carboxylic acid and a carbonyl compound (*vide infra Section 1.4*).¹¹ This visionary reaction then led to Ugi, three decades later, developing his powerful four-component condensation (U-4CR)¹² by the further addition of an amine to the Passerini reaction (P-3CR) (*vide infra Section 1.5*). When taken together, their work laid the foundation of the important area of modern novel isocyanide based multicomponent chemistry.

1.3 Isocyanides.

Isocyanides were first discovered by Lieke in 1859 during an experiment designed to produce allyl cyanide from allyl iodide and silver cyanide.¹³ Whilst attempting acidic hydrolysis of the product which he believed to be allyl cyanide, to a carboxylic acid, he instead produced an *N*-formamide. Further investigation by Lieke into this reaction was discontinued because of constant complaints of a vile odour in the neighbourhood. Indeed without realising it, Lieke had synthesised the first isocyanide - allyl isocyanide; which, along with all other volatile isocyanides has a strange pervading odour. This was described by Gautier as “reminiscent of artichokes and phosphorus at the same time.”¹⁴ Meyer later prepared both methyl and ethyl isocyanide from their iodides by alkylation with silver cyanide, but still did not recognise the structure, instead believing he had produced methyl and ethyl cyanide.¹⁵ Gautier’s later work began to elucidate the structure of these ‘isocyanides’, and on discovering that they were isomers of nitriles, he postulated two structures **7** and **8** (Scheme 2).¹⁶



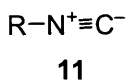
Scheme 2

Twenty-five years later, Nef suggested the following structure **9** to explain the divalent character of isocyanides based upon their observed α -addition reactions (Scheme 3).¹⁷



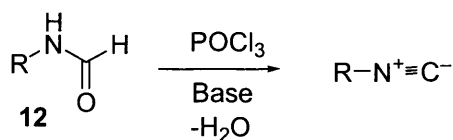
Scheme 3

Finally, the fourth structure **11** was suggested by Lindemann and Wiegrebbe in 1930, which provided the most common graphical representation of an isocyanide used today (Scheme 4).¹⁸



Scheme 4

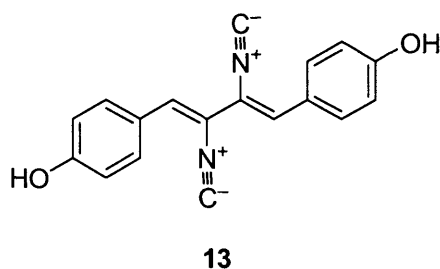
Although the synthesis of phenyl isocyanide from aniline and chloroform in the presence of a strong base by Hoffmann in 1870 opened a route to aromatic isocyanides,¹⁹ it was not until the work of Ugi in 1958, that isocyanides emerged from twelve examples of discrete chemical curiosities into a distinct class of compounds in their own right.²⁰ Thus, Ugi's synthesis of isocyanides from *N*-formamides **12** by dehydration using POCl₃ and a base paved the way for the synthesis of a multitude of isocyanides (Scheme 5).



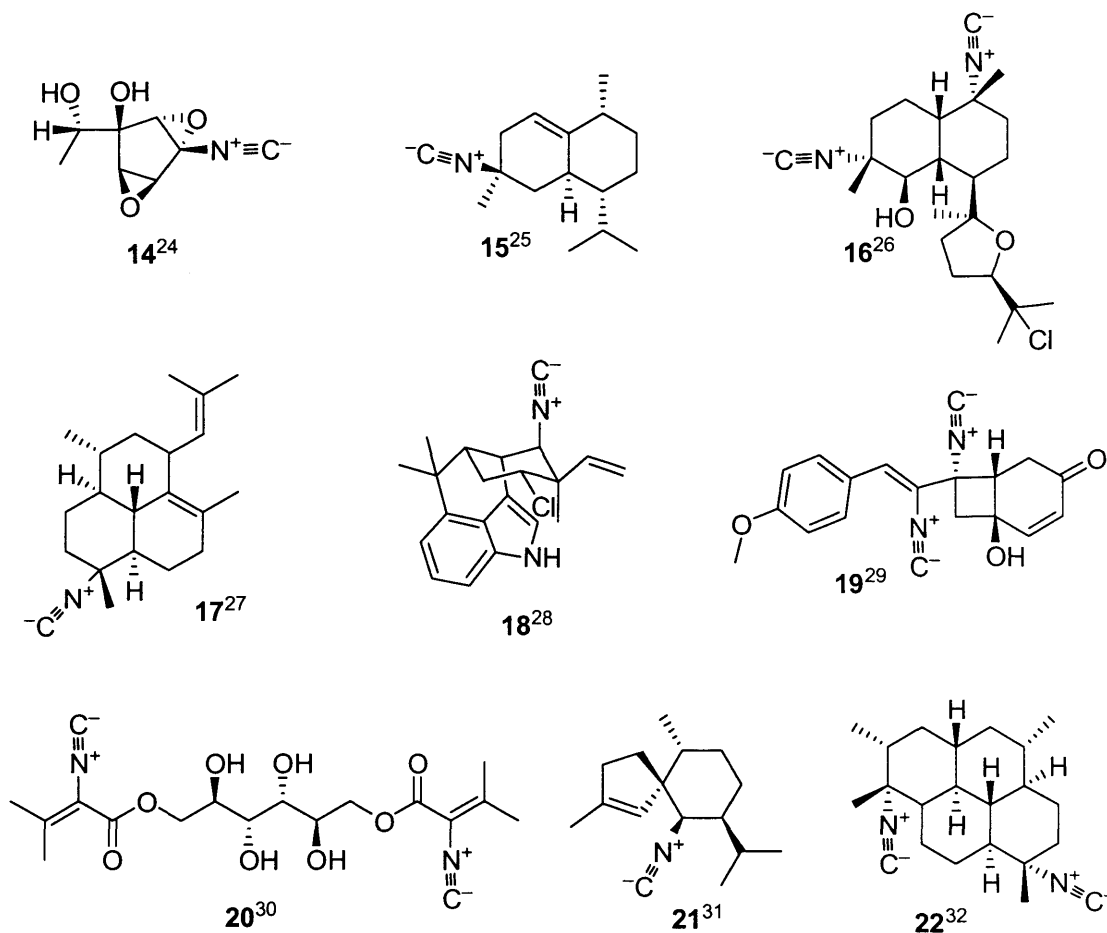
Scheme 5

In the 1960s, the Bayer® Company noted generally low levels of toxicity for isocyanides,²¹ this makes them simple compounds to handle, with the exception of course of the strong odour of volatile examples.

In 1950, Rothe isolated the naturally occurring wide spectrum topical antibiotic Xanthocillin **13**.²²



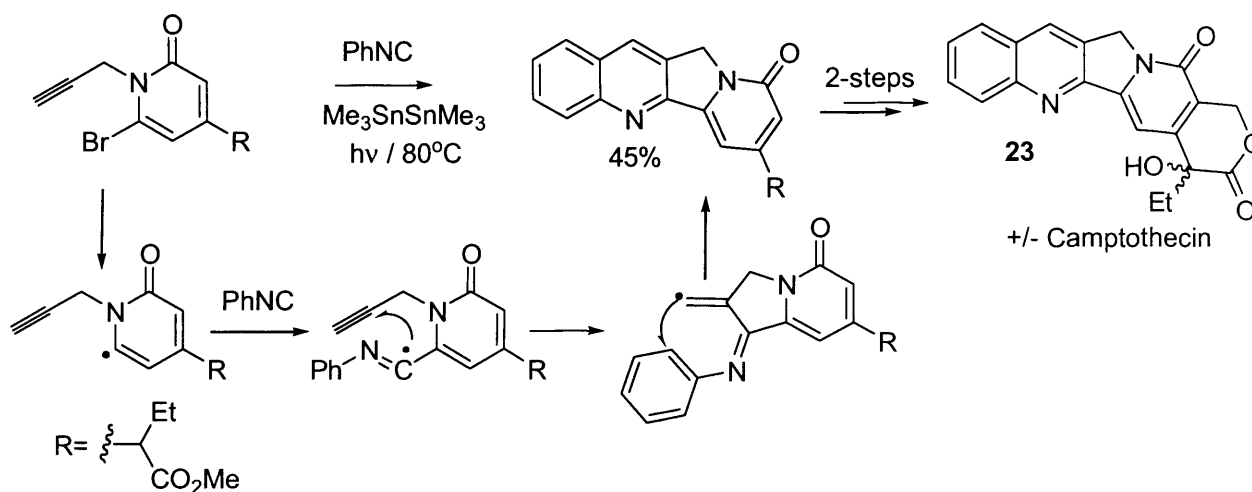
Over the years, the isocyanide functional group has been noted to occur in a wide range of natural products, many of which show distinct antibiotic, fungicidal or insecticidal properties.²³ A plethora of naturally occurring isocyanides have been isolated and characterised, many from marine sources. A few representative examples of these are shown in Scheme 6.



Scheme 6

1.31 The Chemistry of Isocyanides.

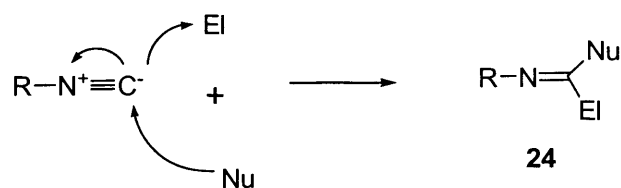
The chemistry of isocyanides is dominated by two distinct and important types of reaction: the α -addition reaction and radical processes. The use of isocyanides in multicomponent chemistry is chiefly concerned with α -additions, and these are discussed in more detail in the next section. Isocyanides have seen use in radical cyclisations as exemplified by Curran's elegant synthesis of the anti-tumour agent Camptothecin **23** *via* a [4+1] radical annulation (Scheme 7).³³ This rich area of chemistry is, however, outside of the scope of this work.



Scheme 7

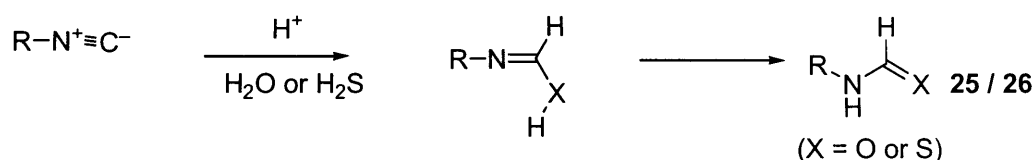
1.311 α -Addition to an Isocyanide

In contrast to conventional addition reactions such as addition of hydrogen bromide to an alkene, in an α -addition to an isocyanide, both nucleophilic and electrophilic constituents form bonds with the isocyanide carbon. A simple mechanism is shown below (Scheme 8).



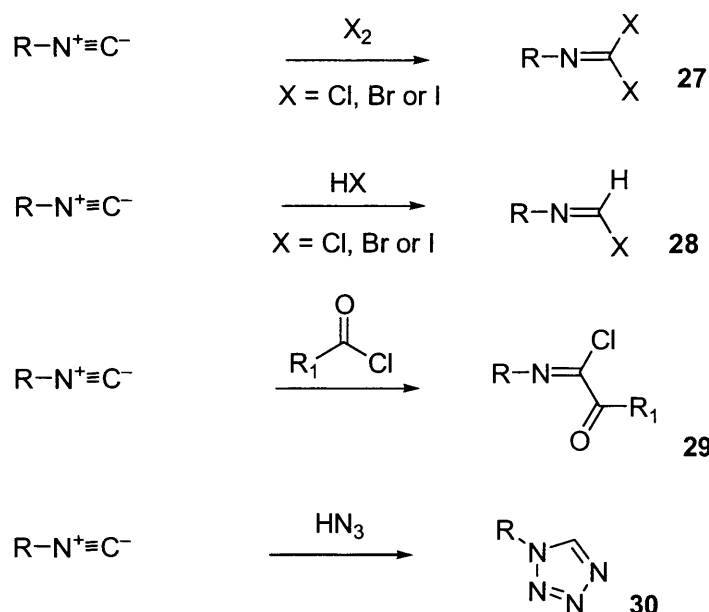
Scheme 8

This reaction may occur in a one-step concerted process, or more usually, in a two-step mechanism. α -Addition to an isocyanide is not dissimilar to the addition reactions undergone by carbon monoxide, which is isoelectronic with the isocyanide motif, and can also be compared with the cheletropic addition of an alkene to a singlet carbene. Isocyanides do not react readily with nucleophiles such as amines and alcohols even under forcing conditions without the use of transition metal catalysis and are stable to alkaline hydrolysis. In contrast, however, they are often attacked by nucleophiles when under the influence of acid catalysis, for example, in the facile acidic hydrolysis of an isocyanide to a formamide **25**,³⁴ or in the reaction with hydrogen sulfide to give a thioformamide **26** (Scheme 9).³⁵



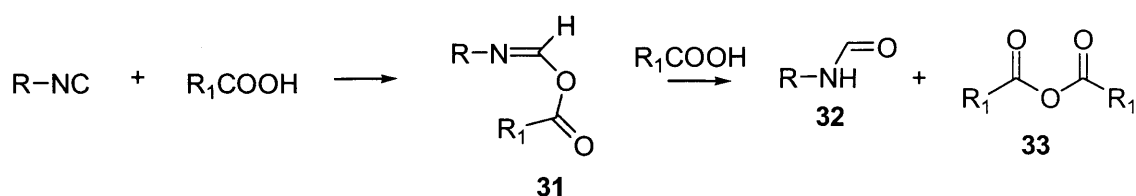
Scheme 9

Isocyanides react willingly with a variety of reagents in simple α -addition reactions without the requirement of an added acid catalyst. The halogens – chlorine and bromine both react violently with isocyanides to give iminocarbamoyl halides **27** (Scheme 10).³⁶ Anhydrous hydrogen halides give formimidoyl halides **28** in a similarly vigorous reaction (Scheme 10).³⁷ Isocyanides react with acid chlorides to afford α -ketoimidoyl chlorides **29** (Scheme 10).³⁸ Hydrazoic acid also reacts with isocyanides to give a good, general preparative method for 1-substituted tetrazoles **30** (Scheme 10).³⁹



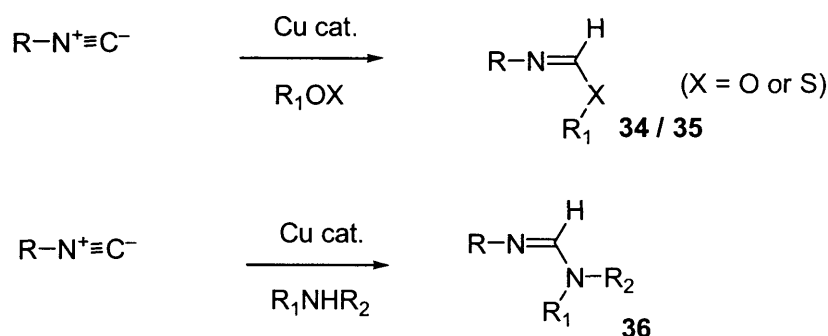
Scheme 10

The reaction between an isocyanide and carboxylic acid gives a mixture of formamide **32** and an acid anhydride **33** (Scheme 11). The α -addition of the carboxylic acid to the isocyanide forms the α -adduct **31**, which then reacts further with another molecule of the carboxylic acid to furnish the formamide **32** and acid anhydride **33**.³⁷



Scheme 11

In the presence of transition metal catalysts, isocyanides will react with a further variety of compounds which will not otherwise react at all. Alcohols and thiols react readily to form formidates **34** and thioformimidates **35** with Copper catalysts (Scheme 12).^{37,40,41} Amines will also react with an isocyanide under Cu(I) catalysis, forming a formamidine **36** (Scheme 12).⁴²



Scheme 12

The frontier molecular orbital descriptions of an isocyanide and carbon monoxide highlight why the α -addition, which occurs on the carbon atom of an isocyanide and carbon monoxide is in stark contrast to the reactivity of a nitrile (Figure 1).⁴³ The large π^* LUMO orbital coefficient on the isocyanide and carbon monoxide carbon atom explains the electrophilic nature of the carbon on both of these moieties, enabling them to accept electron density into the π^* LUMO orbital from a suitable Lewis base or nucleophile. Simultaneously, the σ HOMO-1 of an isocyanide or carbon monoxide may donate electron density to a suitable Lewis or Brønsted acid, thus also concurrently rendering the same carbon atom nucleophilic.

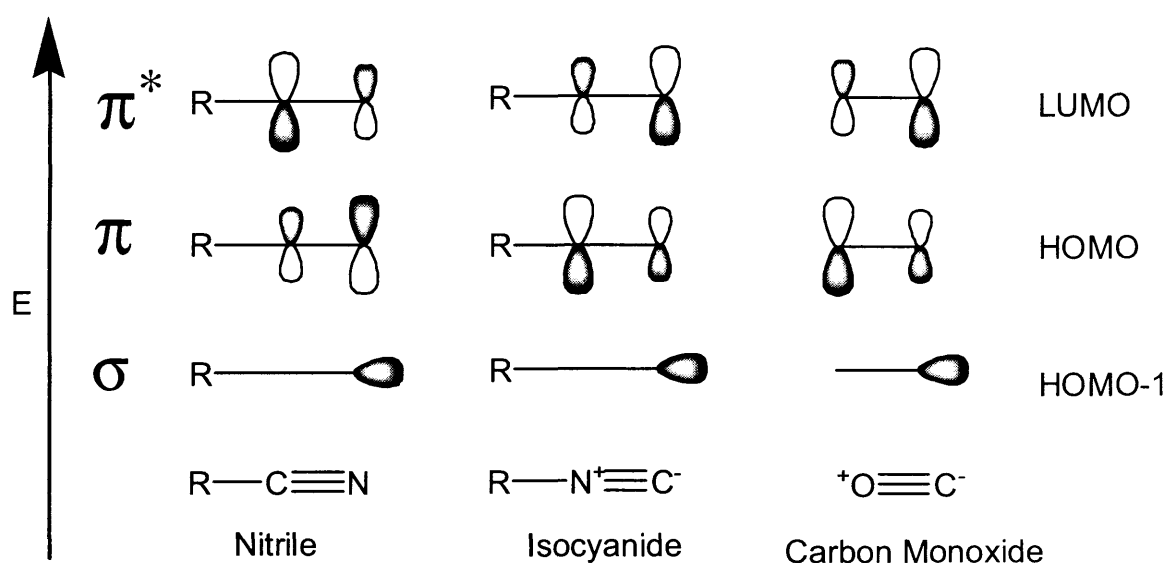


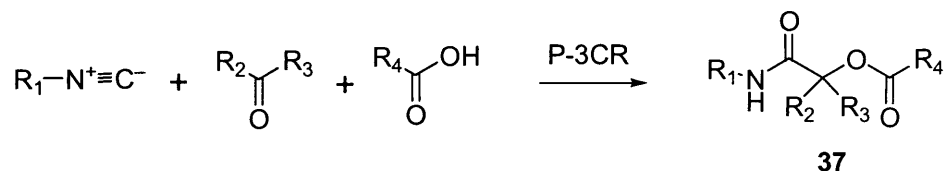
Figure 1. Frontier molecular orbitals of a nitrile, isocyanide and carbon monoxide.

1.312 Isocyanide Based Multicomponent Reactions (IMCRs).

Whilst many of the aforementioned α -addition reactions are synthetically useful in their own right, it is in the area of multicomponent reactions where the unique reactivity of the isocyano group really comes into its own. Isocyanides are perfectly geared up towards acting as the centrepiece in often complex multi-compound condensation reactions. Many isocyanide based multicomponent reactions (IMCRs) have been described in the last century, most of these being variations on a theme of the two classic isocyanide based multicomponent reactions - the Passerini and Ugi reactions.

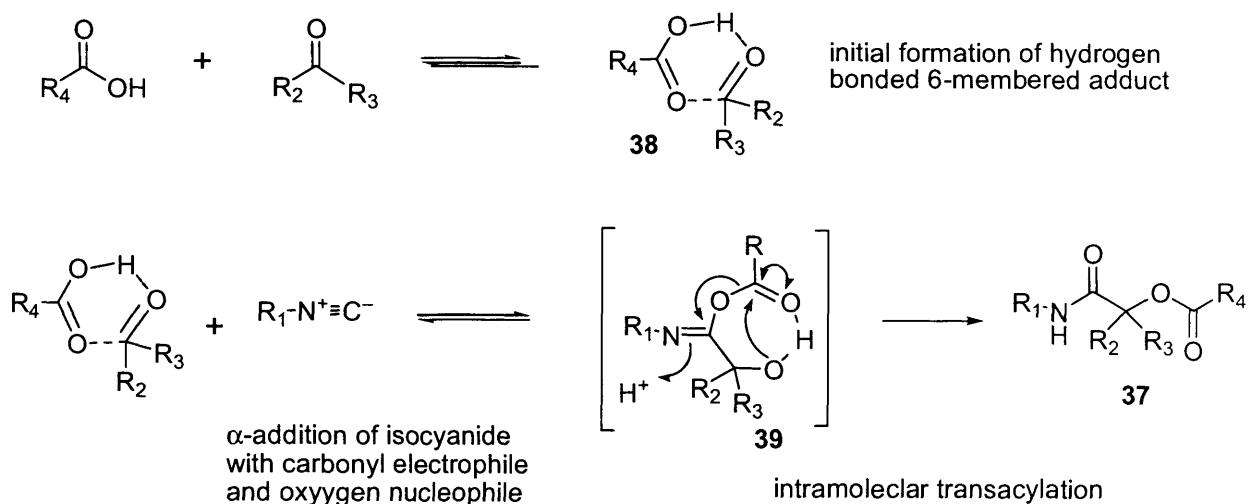
1.4 Passerini Three-component Reaction (P-3CR).

Passerini described the first important isocyanide based multicomponent reaction (IMCR) in 1921,¹¹ in which an isocyanide, a carboxylic acid and a carbonyl compound all react to produce an α -acyloxycarboxamide **37** (Scheme 13).



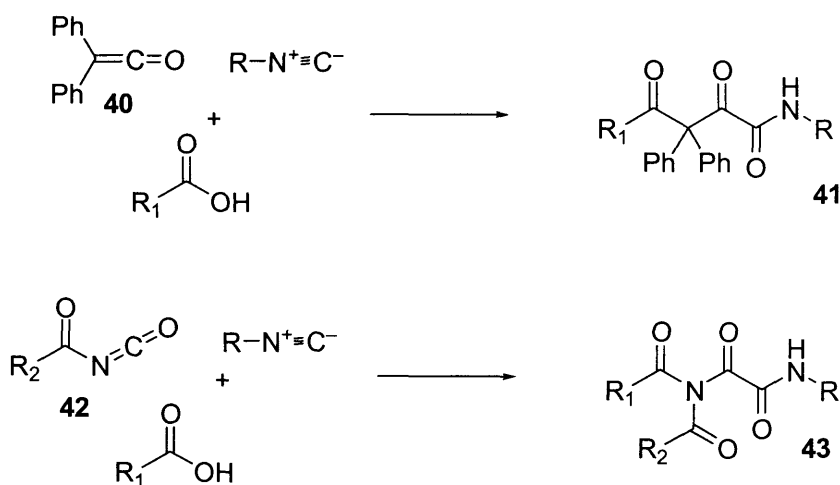
Scheme 13

Several mechanisms have been suggested, but due to the observed retardation of the rate of the reaction by polar and protic solvents, a non-ionic concerted mechanism has been put forward to be the most likely (Scheme 14).¹ The irreversible final *O*-acyl migration step makes this reaction a type II MCR (*vide supra*, Table 1). The previous α -addition step is also quasi-irreversible due to the strongly exothermic nature of the isocyanide C^{II} to C^{IV} transition, which, in common with most preparative IMCRs drives the equilibrium to the right making them type II.



Scheme 14

Whilst the use of aldehyde and ketone substrates is significantly more common, ketenes⁴⁴ **40** and acyl cyanates⁴⁵ **42** have also been used as the oxygen-containing component in a P-3CR (Scheme 15).



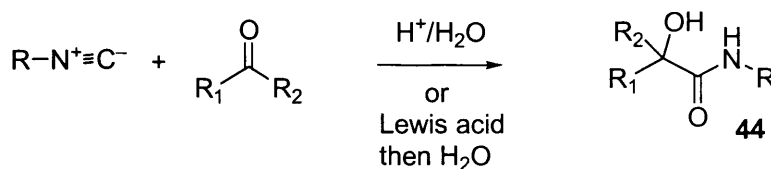
Scheme 15

1.41 Alternative Nucleophiles to Carboxylic Acids in the Passerini

Reaction (P-3CR).

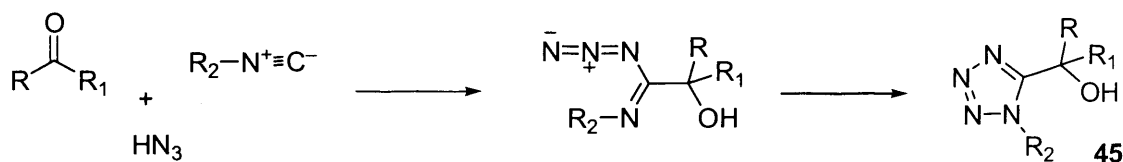
In the absence of a carboxylic acid, a Lewis acid such as $\text{BF}_3 \cdot (\text{Et}_2\text{O})$, followed by an aqueous workup or use of an aqueous, protic acid allows water to act as the

nucleophilic component of a P-3CR to give an α -hydroxyamide product **44** (Scheme 16).⁴⁶ The α -adduct in this case, is stable and no rearrangement reaction is therefore required to drive the reaction to preparative completion.



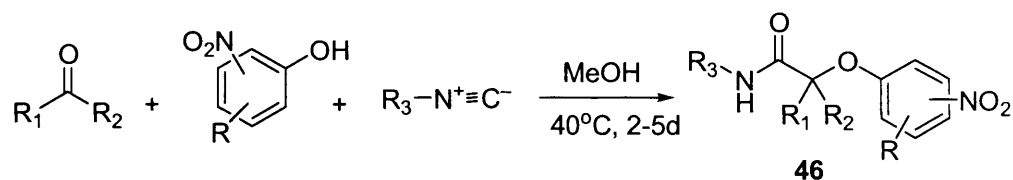
Scheme 16

Hydrazoic acid may be used in the place of a carboxylic acid in the P-3CR to give disubstituted hydroxytetrazoles **45** (Scheme 17).⁴⁷ However, this reaction only gives appreciable yields in cases with highly reactive carbonyl components, since in less reactive examples the competing formation of tetrazoles from the aforementioned α -addition between hydrazoic acid and isocyanides dominates (*vide supra*, Scheme 10). This undesirable side reaction may be prevented by the use of aluminium azide in the place of hydrazoic acid.⁴⁷



Scheme 17

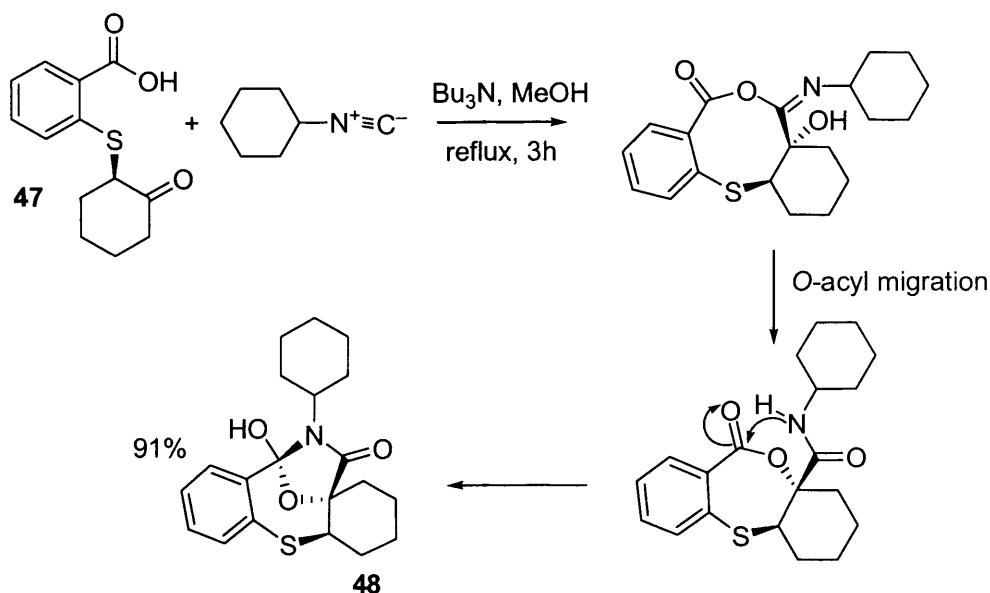
Following their recently published Ugi type process⁴⁸ utilising electron deficient phenols in the place of carboxylic acids *via* a Smiles rearrangement⁴⁹ (*vide infra*, Scheme 64), El Kaim and Grimaud have recently produced a three-component addition of an isocyanide to a nitrophenol and carbonyl compound (Scheme 18).⁵⁰ The mechanism is proposed to involve an ionic mechanism in contrast to a classical Passerini reaction in a non polar aprotic solvent, with an ensuing Smiles rearrangement.⁴⁹



Scheme 18

1.42 Stereocontrol in the P-3CR.

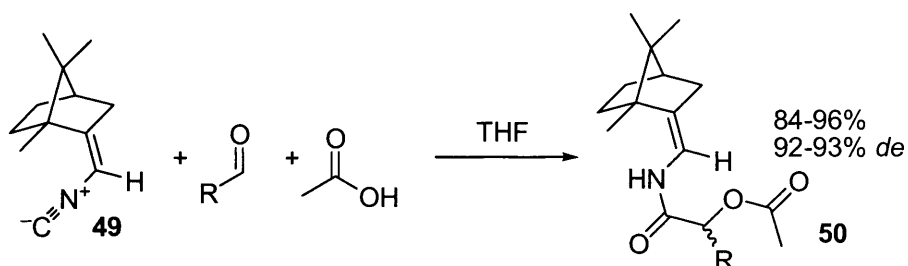
A P-3CR using a prochiral carbonyl substrate will generate a new chiral centre in the α -acyloxyamide product **37**. The concerted mechanism means that all three starting materials are involved in cyclic transition state **39**, and therefore it should be possible to achieve asymmetric induction *via* the use of any enantiomerically enriched substrate. The use of chiral carbonyl starting materials results in poor diastereoselectivity, probably due to the low steric demand of the adjacent linear isocyanide in the transition state **39**.² However the use of chiral keto-acid **47** results in exclusive formation of only one diastereomer **48** (Scheme 19).⁵¹



Scheme 19

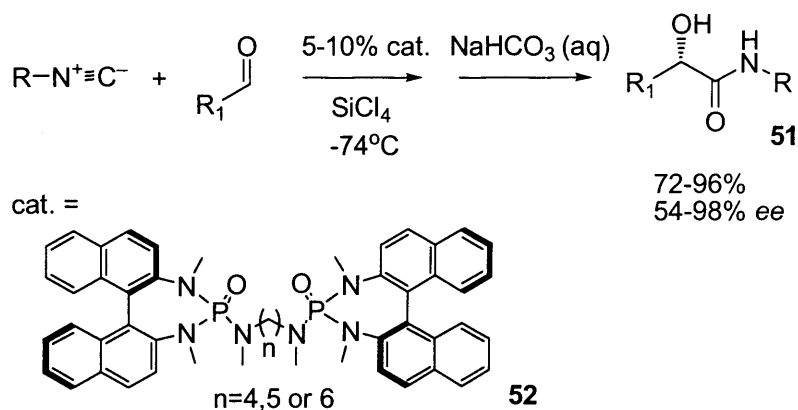
Most isocyanides lead to little diastereoselectivity, however, the camphor derived example **49**, gives good levels of asymmetric induction in the product **50** (Scheme 20).⁵² This vinylic isocyanide **49** may be cleaved under mild acidic conditions to

yield either an acid or an ester and is therefore representative of a useful chiral auxiliary for the asymmetric P-3CR.



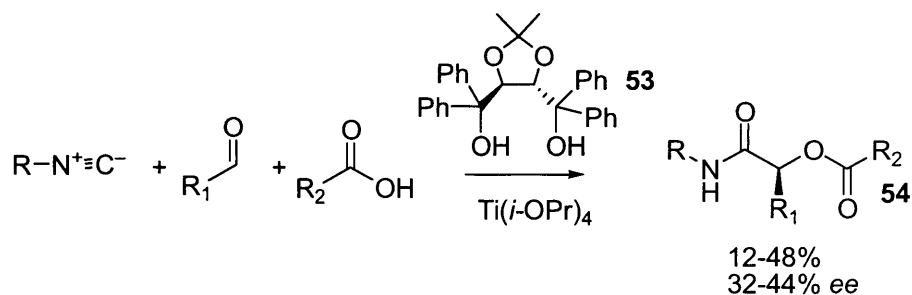
Scheme 20

The use of a chiral catalyst has also been shown to achieve asymmetric control in the Passerini reaction. However, in the first studies the chiral catalyst was present as a Lewis acid, replacing the carboxylic acid component, and thus, the product, after aqueous workup was an α -hydroxyamide **51**. The first catalytic asymmetric α -addition to isocyanides was demonstrated by Denmark and Fan in this manner, using a chiral phosphoramidate Lewis base **52** to activate the weak SiCl_4 Lewis acid achieving moderate to excellent enantiomeric excesses (Scheme 21).⁵³



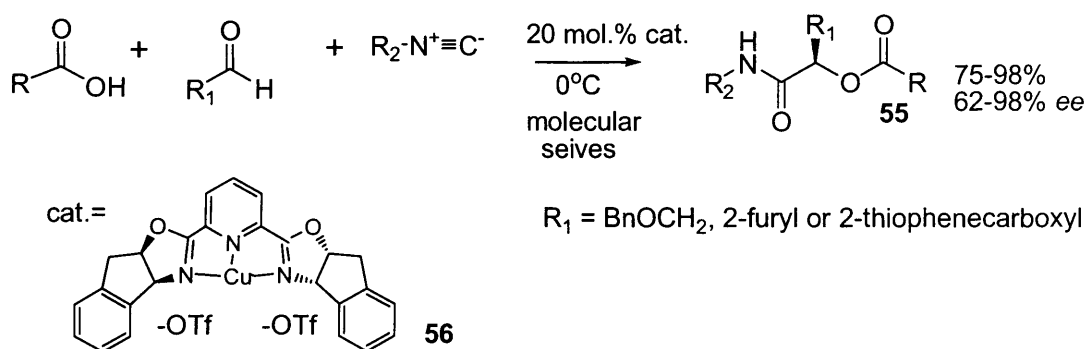
Scheme 21

Following an extensive catalyst screening using parallel methods, Domling *et al.* published the first asymmetric P-3CR from three achiral starting materials *via* stereochemical induction by a Lewis acid / chiral catalyst **53** combination (Scheme 22).⁵⁴ However, a strictly limited number of model substrates are shown and only a moderate enantiomeric excess has thus far been demonstrated.



Scheme 22

More recently a P-3CR under Lewis acid chelation control using a tridentate Indian (pybox) bulky chiral Cu(II) derived Lewis acid catalyst **56** has been reported by Schreiber (Scheme 23).⁵⁵ Enantiomeric excesses of up to 98% were achieved for aldehydic substrates with functionality capable of bidentate coordination, such as the examples shown in Scheme 23.

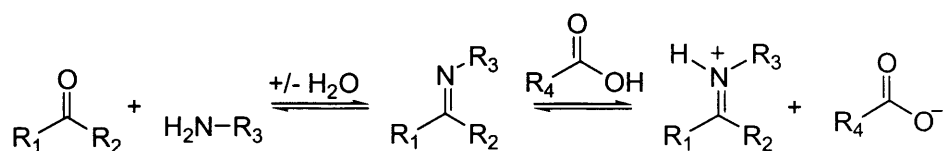


Scheme 23

1.5 Ugi Four-Component Condensation (U-4CR).

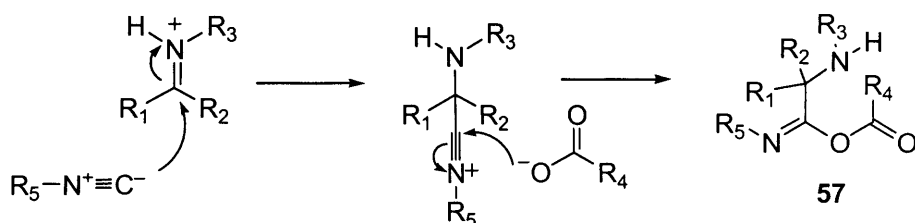
In 1959, Ugi published his classic four-component condensation reaction between a primary amine, a carbonyl compound, an acid and an isocyanide.¹² The use of extended systems of chiral substrates and reactions led to an indecipherable and seemingly endless supply of data, such that an early Zuse computer was used to provide a simplified reaction mechanism.^{1, 56, 57}

Fast initial imine formation takes place by the simple reaction of an amine with a carbonyl compound *via* the hemiaminal (Scheme 24).



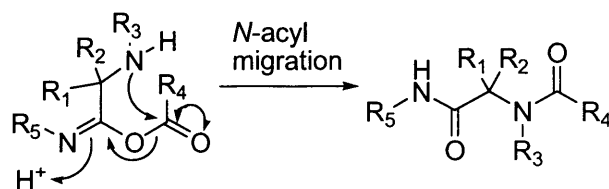
Scheme 24

After imine formation, the Ugi reaction could just be thought to be an aza-analogue of the Passerini reaction. However, experimental evidence shows that an entirely different mechanism is occurring. The imine is activated towards nucleophilic attack by protonation to afford an iminium ion. Subsequent α -addition leads to an unstable α -acyloxy imine adduct **57** (Scheme 25).



Scheme 25

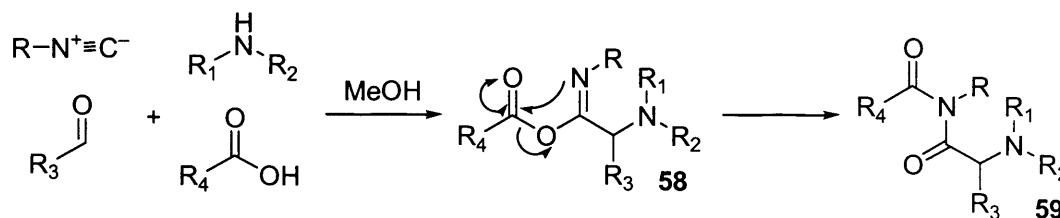
The α -addition has been postulated as a two-step sequence,^{56,57} where the iminium ion undergoes nucleophilic attack by the isocyanide, and this intermediate, in turn, is attacked by the acid component. In cases where this does not form a stable α -aminoalkylation product, an *N*-acylation occurs intramolecularly *via* a 6-membered intermediate *c.f.* the final step of the Passerini reaction (Scheme 26).



Scheme 26

When a secondary amine is employed in the U-4CR, the amine nitrogen in the α -adduct **58** is tertiary and therefore cannot take part in an *N*-acyl migration as detailed

above. If the reaction is carried out in anhydrous methanol, the nitrogen atom of the imino-anhydride **58** is acylated to furnish an acylamide **59** (Scheme 27).⁵⁸



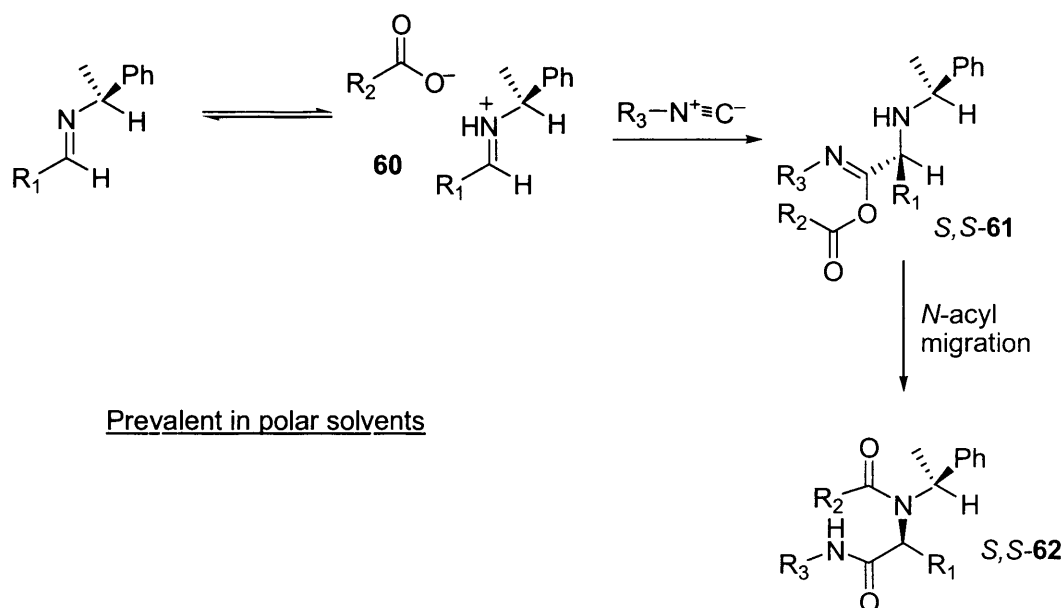
Scheme 27

1.51 Stereocontrol in the Ugi Reaction (U-4CR).

Chiral isocyanides offer little to no asymmetric induction in the U-4CR. For example, when the chiral camphor derived isocyanide **49**, which as previously discussed gives excellent diastereoselectivity in the P-3CR (Scheme 20), is used in the U-4CR, no selectivity at all is observed.⁵⁶ This led to the suggestion that the isocyanide is not involved in the step which determines the configuration of the new chiral centre.⁵² Moreover, at present there are no reports of significant stereochemical induction by the use of a chiral carboxylic acid component. In similar fashion, carbonyl compounds are often only capable of moderate degrees of asymmetric induction for the U-4CR even for examples which would give good stereochemical induction with other nucleophiles.²

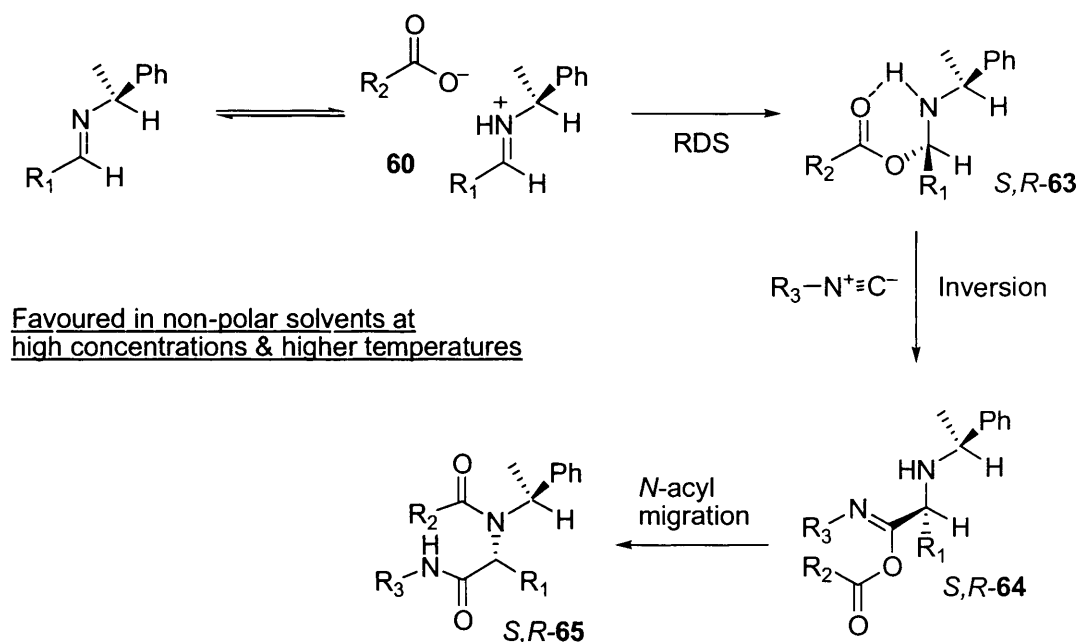
Conversely, when chiral amines are employed in the asymmetric U-4CR, either the *R* or *S* diastereomer is formed depending on the reaction conditions. Temperature and concentration changes can completely invert the selectivity. α -Methylbenzylamines have been used many times as chiral auxiliaries in order to control the formation of a new chiral centre, and these directing groups can, of course then be simply removed by subsequent hydrogenolysis.⁵⁹ In 1967, Ugi and co-workers suggested at least two competing mechanistic pathways to be in operation in an asymmetric Ugi reaction by employing (*S*)- α -methylbenzylamine as a bulky chiral directing group.^{60,61} Schemes

28, 29 and 30 show three potential mechanisms in order to explain the differing selectivity observed by varying reaction conditions.⁶² In mechanism A (Scheme 28), the established Ugi mechanism, the isocyanide must preferentially attack from the less sterically shielded bottom face of **60** leading to (*S*)-(*S*)-**61** and subsequently (*S*)-(*S*)-**62** as the product. (Note – nomenclature assumes R_1 = lowest priority).



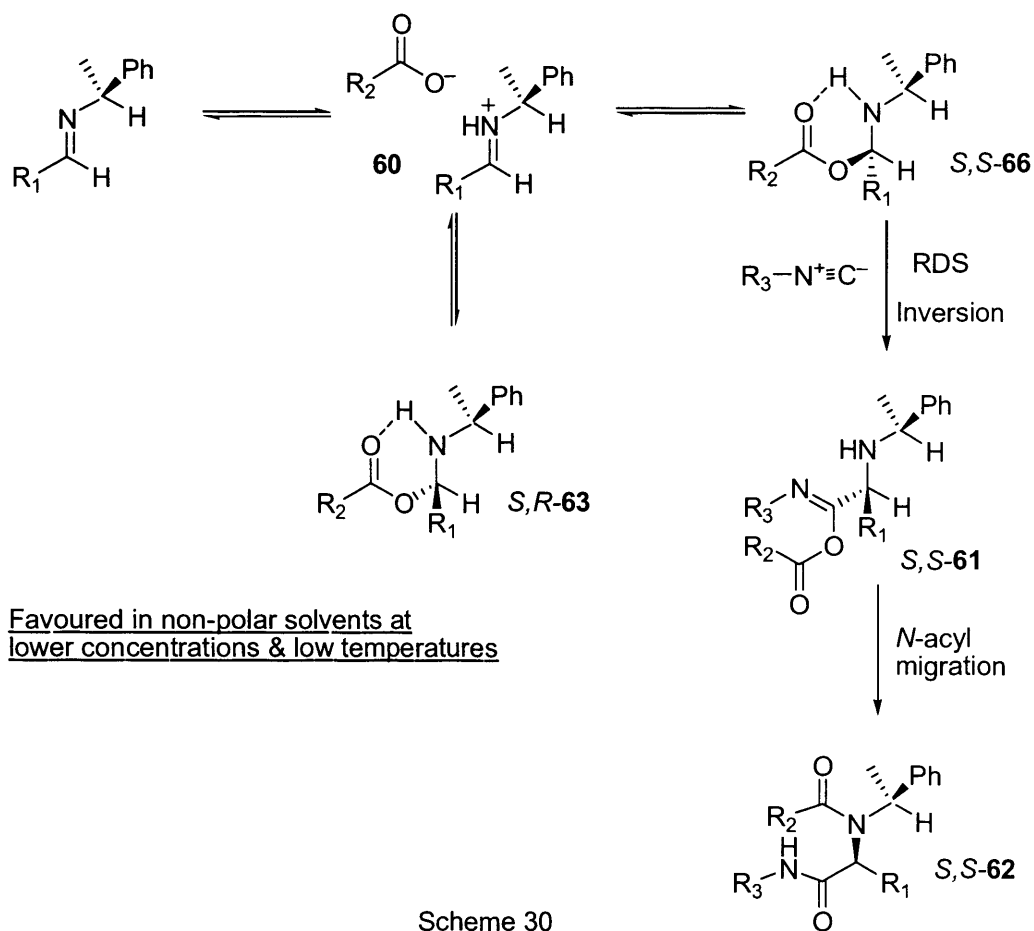
Scheme 28

Mechanism B (Scheme 29) shows a similar mechanism to the Passerini reaction (P-3CR), in which the carboxylate forms a hydrogen bonded complex **63**. At this stage insertion by the isocyanide with resultant inversion gives the (*S*)-(*R*)-intermediate **64**, which undergoes *N*-acyl migration to give the (*S*)-(*R*)-product **65**.⁶⁰ This pathway may explain the lack of asymmetric induction by chiral isocyanides, since the isocyanide is not involved in formation of the initial reversible intermediate **63**.



Scheme 29

The third pathway – mechanism C (Scheme 30) suggests that the reversible formation of the hydrogen bonded intermediate **63** is not the rate determining step, but in fact the isocyanide insertion is fast and irreversible and occurs before the hydrogen bonded complex can equilibrate to the lower energy (S) - (S) -complex **66**. In this example, formation of the (S) - (R) -intermediate **63** is kinetically more favourable on steric grounds, but (S) - (S) -**66** is lower in energy and thus thermodynamically favoured due to the destabilising interaction between Ph and R_1 in the (S) - (R) intermediate diastereoisomer **63**. Therefore (S) - (S) -**62** would be expected to be formed preferentially after the final irreversible N -acyl migration step has occurred.



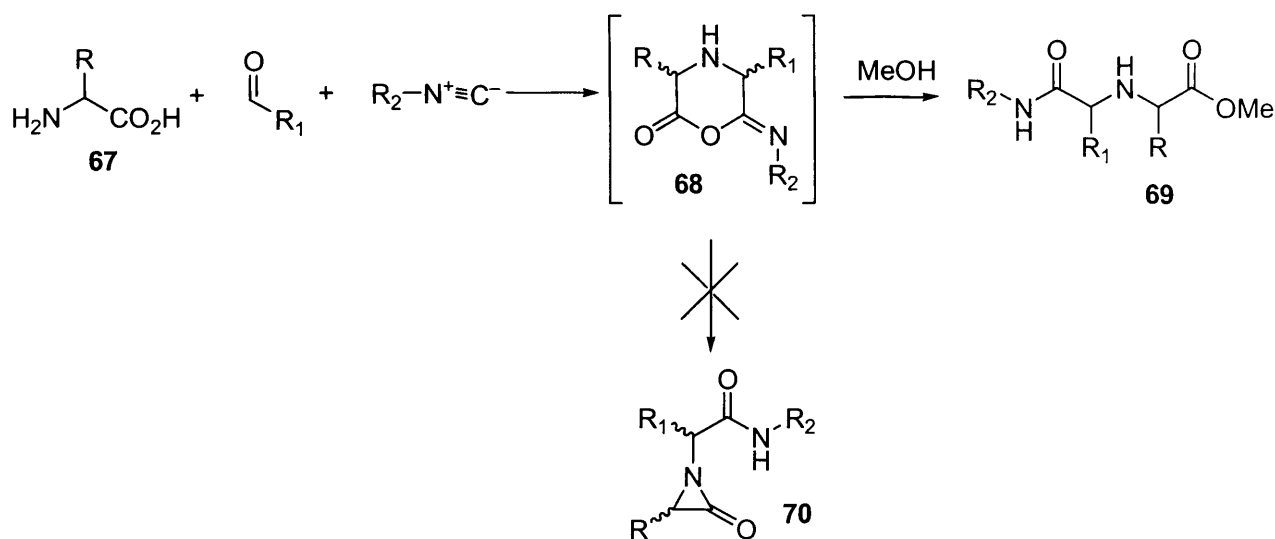
At low reactant concentration, mechanism C prevails over B, whilst at higher concentrations, (*S*)-(*R*)-**65** is formed in greater amounts *via* mechanism B. This is because an increase of the isocyanide concentration in mechanism B should increase the rate of isocyanide attack thereby making the formation of the hydrogen bonded complex the rate determining step (RDS). Lower reaction temperatures favour formation of (*S*)-(*S*)-**62**, which may be explained by the fact that pathways A and C are more entropically disfavoured than B. Therefore the decrease in reaction rate with temperature is lower for pathway B, since the $-T\Delta S$ component of the Gibbs equation ($\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$) is less significant.⁶² Pathway A is expected to dominate over B & C in polar solvents since, similarly to the Passerini reaction mechanism, polar solvents retard the rate of this mechanism which requires the formation of cyclic hydrogen bonded intermediate.

1.52 Ugi Reactions Using Bifunctionalised Starting Materials.

Although a good degree of diversity may be achieved using the simple U-4CR by variation of the substituents on each of the components, the resulting structural framework remains constant. Efforts have therefore been made to broaden the scope of the reaction by using bifunctional starting materials.

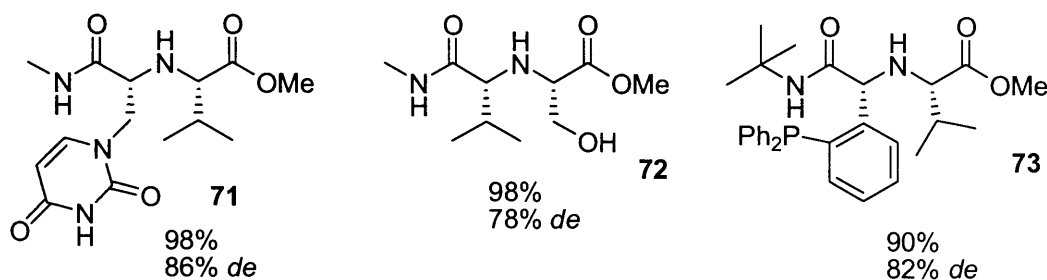
1.521 Amino-acids in U-4CR.

Initial unpublished studies by Steinbruckner and Ugi into the use of α -amino-acids in an U-4CR to produce α -lactams **70** were, not surprisingly unsuccessful. Since the non-isolable six-membered α -adduct **68** is not capable of $O \rightarrow N$ acyl migration due to ring strain (Scheme 31).⁶³ Instead, solvent participation by methanol *via* nucleophilic attack on **68** results in a secondary amine product **69**.



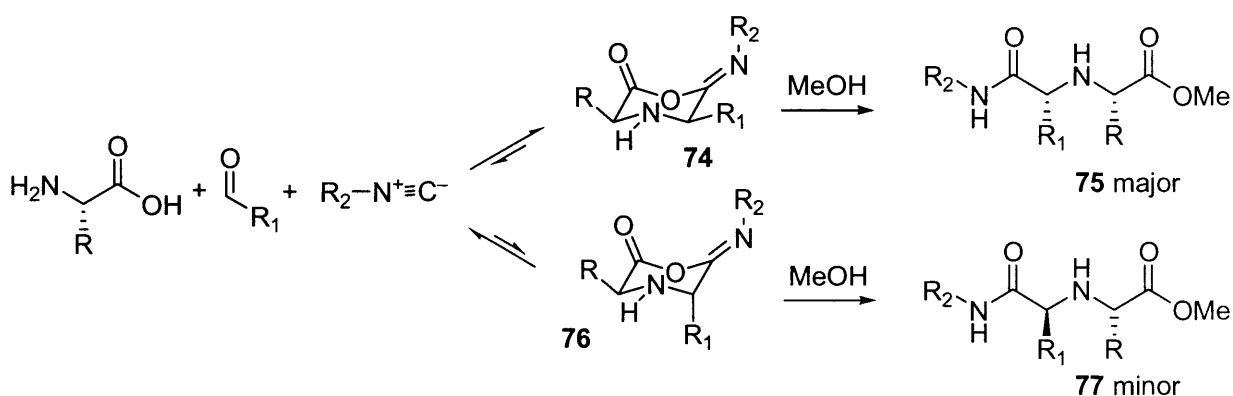
Scheme 31

A vast array of α -amino-acids may undergo this reaction, usually in over 95% yield.⁶⁴ In addition, the formation of the new chiral centre proceeds with good diastereoselectivity (see examples in Scheme 32).^{65, 66}



Scheme 32

This high level of diastereoselectivity may be explained by the reversible, thermodynamic formation of the cyclic intermediate **68**. When the α -amino acid has a sterically demanding side chain $-R$, this will preferentially sit in an equatorial position, and conformation **74** will therefore be lower in energy than conformation **76** due to the reduced steric repulsion. The rate of formation of the different diastereomers will therefore be dependant on the relative population of intermediates **74** / **76**. In consequence, the use of less sterically demanding R -groups generally results in lower diastereoselectivity (Scheme 33).⁶⁵

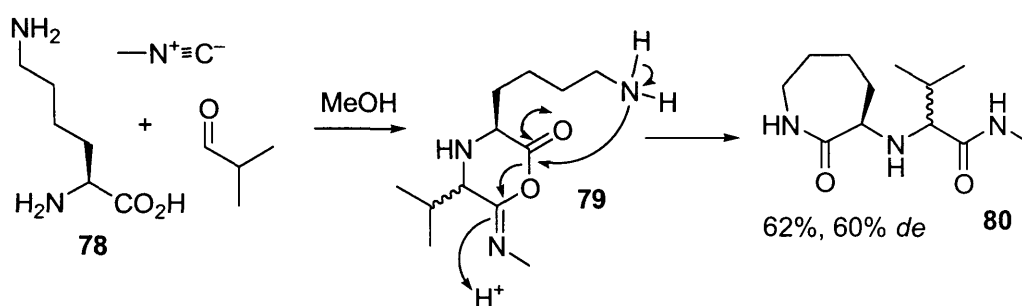


Scheme 33

Ugi *et al.*, further suggested that the diastereoselectivity can be controlled by temperature and use of metal catalysts, but did not publish any further examples or data to this effect in the primary literature.⁶⁷ It was also reported that other classes of compounds, other than alcohols, such as amines and thiols can react as nucleophiles

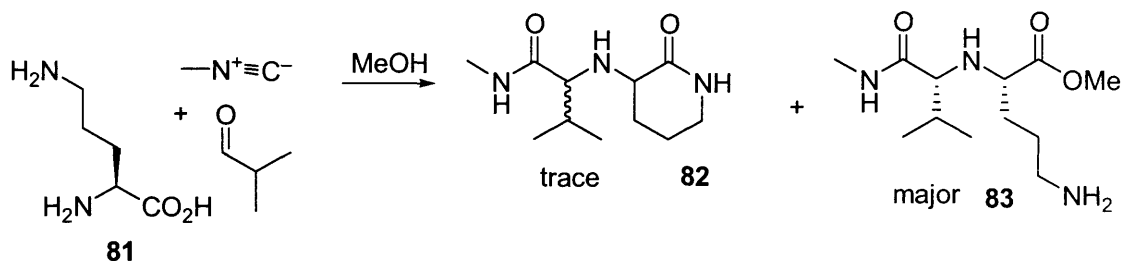
in the U-5C-4CR although sadly no given examples were cited in this piece of work.⁶⁸

When a trifunctionalised α -amino acid is applied to this reaction, the pendant nucleophilic side group may, in certain cases, attack the unstable α -adduct **68**.⁶⁹ Use of *L*-Lysine **78** results in the formation of a ϵ -lactam **80**, either *via* attack on the *O*-acylamide intermediate **79** by the pendant side chain amino group with resultant rearrangement, or by nucleophilic substitution of the standard U-5C-4CR ester product by the ϵ -amino functionality (Scheme 34).⁶⁹



Scheme 34

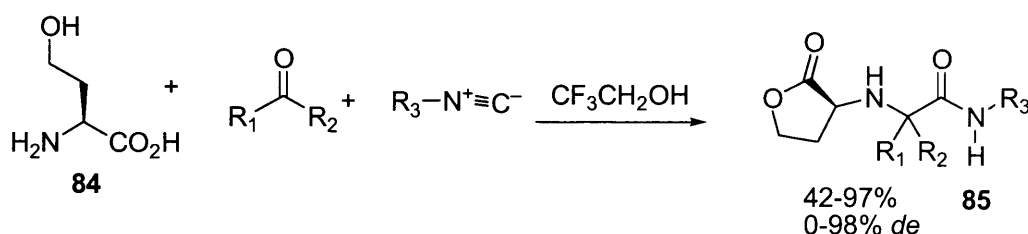
However due to steric constraints, the use of *L*-ornithine **81** which has one fewer methylene units in the side chain only resulted in the formation of traces of the corresponding δ -lactam **82**. Instead **83** was isolated as the major product (Scheme 35).⁶⁹



Scheme 35

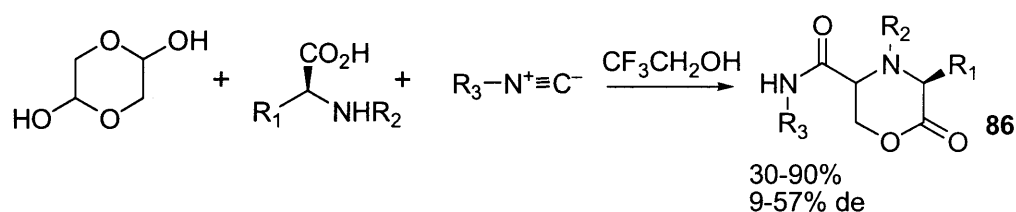
When homoserine **84** was selected as the α -amino acid substrate in the less nucleophilic solvent – trifluoroethanol, *N*-carbamoylmethyl- α -aminobutyrolactones

85 were produced by participation of the γ -hydroxyl group, instead of the alcoholic solvent (Scheme 36).⁷⁰ Serine and threonine are not reported to react *via* this pathway.⁷⁰



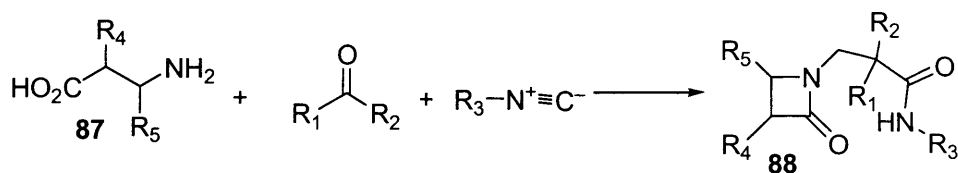
Scheme 36

A multicomponent approach to novel 3-substituted morpholine-2-one-5-carboxamides **86** using glycolaldehyde dimer as the 'carbonyl' constituent, an α -amino acid and an isocyanide in an Ugi five-centred, four-component reaction (U5C-4CR) has been developed by Kim (Scheme 37).⁷¹ Although optimal yields were achieved using 2,2,2-trifluoroethanol, increased diastereoselectivity (5:1 and 3:1 respectively) was observed with the use of $ZnCl_2$ as an activating Lewis acid in MeOH or THF.



Scheme 37

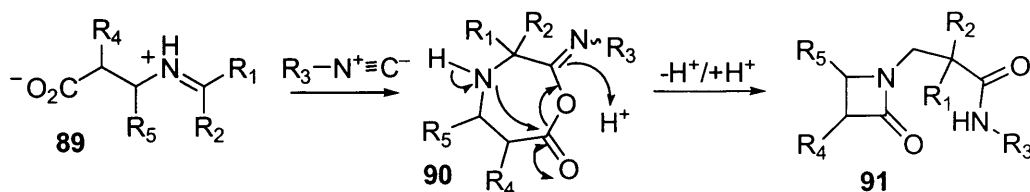
In 1961, Steinbrückner demonstrated an isocyanide based multicomponent approach to β -lactams using β -amino acids **87** in a U-4C-3CR (Scheme 38).⁷²



Scheme 38

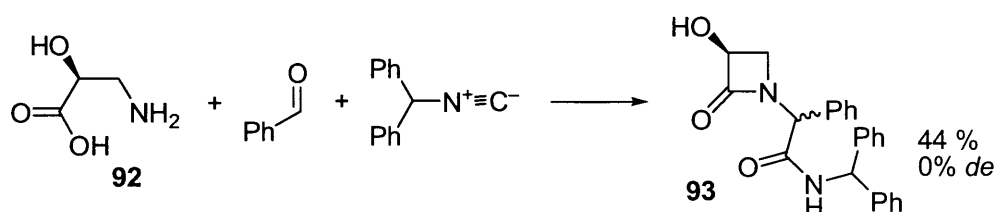
The immonium betaine **89**, undergoes fast ring closure on the nitrilium cation produced by the isocyanide attack. The intermediate cyclic α -adduct **90** is

sufficiently conformationally flexible to undergo spontaneous quasi-irreversible transannular acylation to furnish the stable β -lactam **91** (Scheme 39).



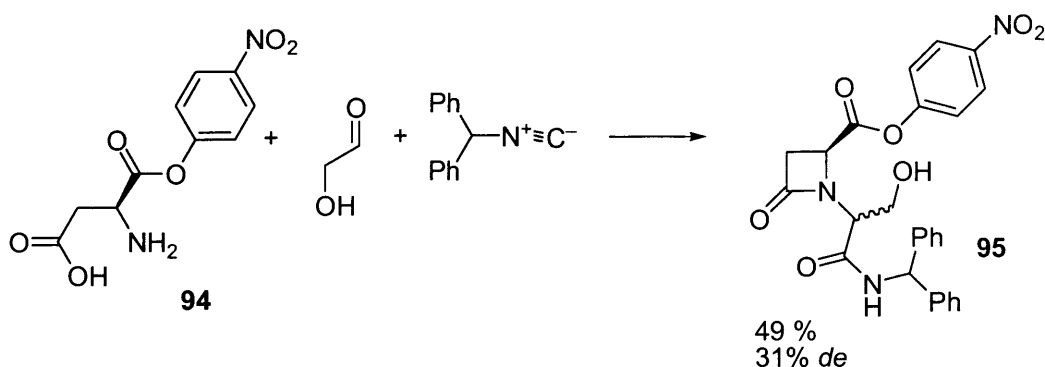
Scheme 39

Little to no diastereoselectivity is achieved when the stereogenic centre is at the α -position of the β -amino acid *e.g.* **92**, due to the distance between the two chiral centres in the seven-membered intermediate **90** (Scheme 40).⁷³



Scheme 40

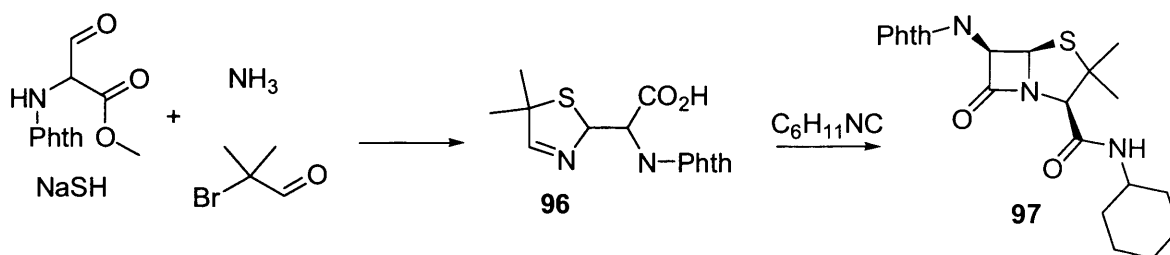
However, when the β -position is chiral **94**, a slightly greater degree of diastereomeric control is observed (Scheme 41).⁷³



Scheme 41

The preparation of a penicillin derivative **97** was carried out using this methodology by Ugi and Wischofer in 1962, using an Asinger four-component reaction (A-4CR)⁷⁴ and a subsequent Ugi reaction of the resultant thiazoline **96** (Scheme 42).⁷⁵ This

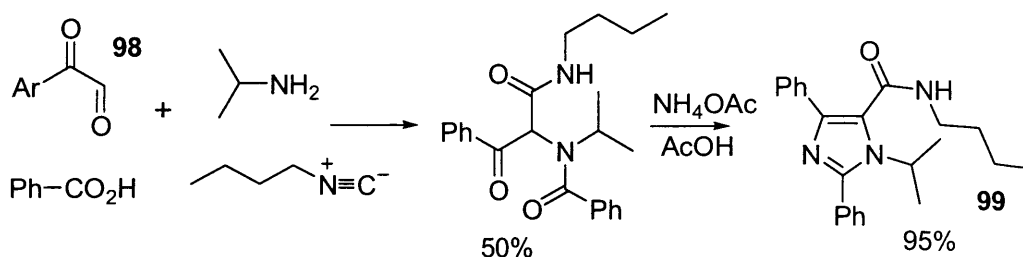
represents the first example of the union concept of sequential combinations of multicomponent reactions.



Scheme 42

1.522 Dicarboxyl Substrates in the Ugi Reaction.

The U-4CR of arylglyoxals **98**, 1° amines, carboxylic acids and isocyanides with subsequent cyclisation was shown to be an efficient method for the preparation of substituted imidazoles **99** (Scheme 43).⁷⁶

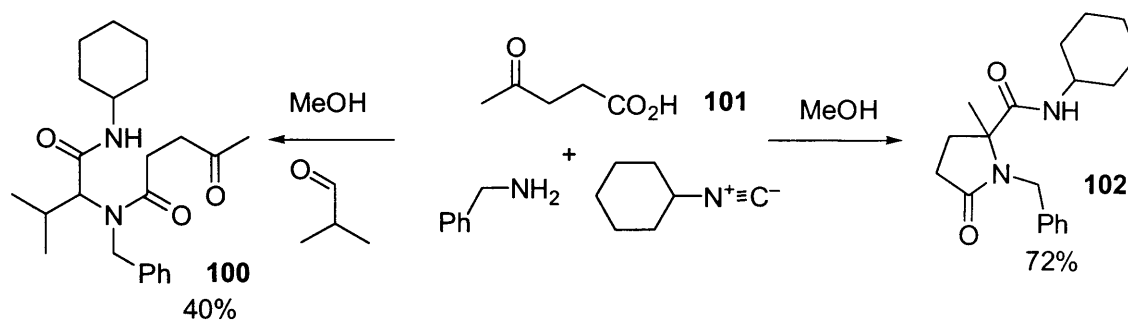


Scheme 43

This reaction has also been carried out on a modified Wang resin as the isocyanide component with subsequent cleavage by TFA to yield a terminal carboxylic acid.⁷⁷

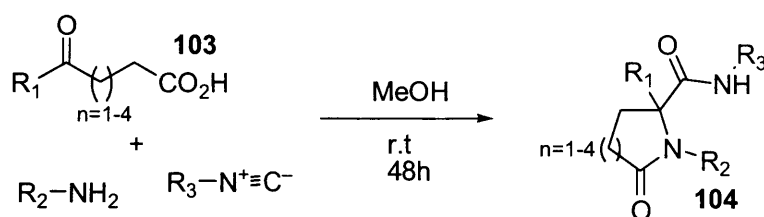
1.523 Carbonyl-Carboxylic Acid Substrates in the Ugi Reaction.

Ketoacids as bifunctionalised substrates for the Ugi reaction had been investigated and published as early as 1968.⁷⁸ Gross *et al.* demonstrated the use of levulinic acid **101** with benzylamine and cyclohexyl isocyanide to give a five membered lactam product **102** (Scheme 44). Interestingly, when this reaction is carried out in the presence of isobutyraldehyde, the normal Ugi product **100** is formed exclusively.⁷⁸



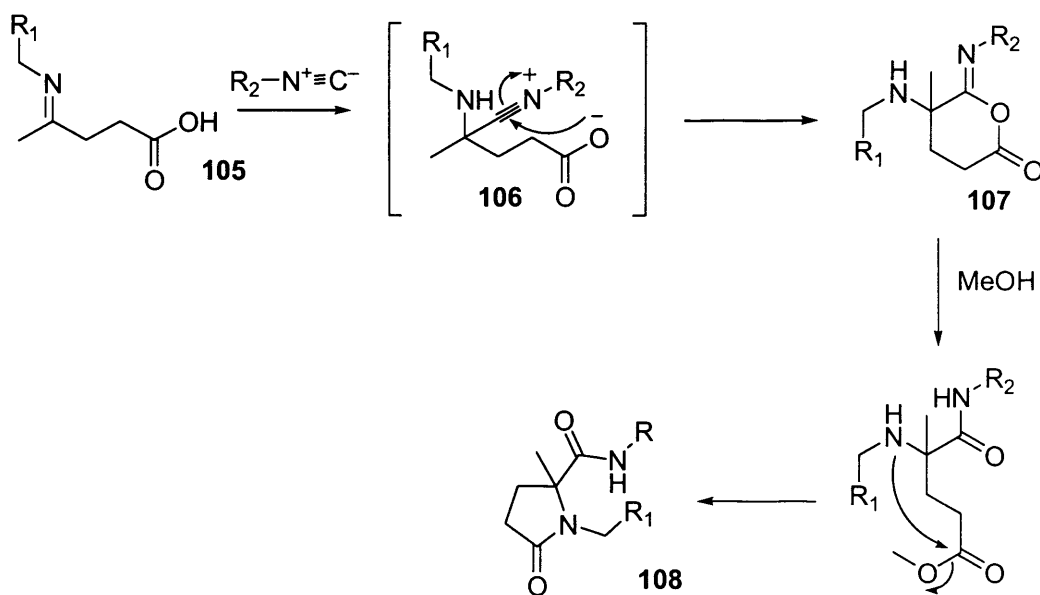
Scheme 44

More recently, in 1997, Short and Mjalli at Ontogen Corp.[®] published the facile preparation of a further selection of five and six membered ring lactams by the U-4C-3CR of ketoacids **103**, isocyanides and primary amines.⁷⁹ Later in the same year, this work was extended by a second group to allow preparation of seven and eight membered lactams through the use of highly dilute reaction conditions (Scheme 45).⁸⁰



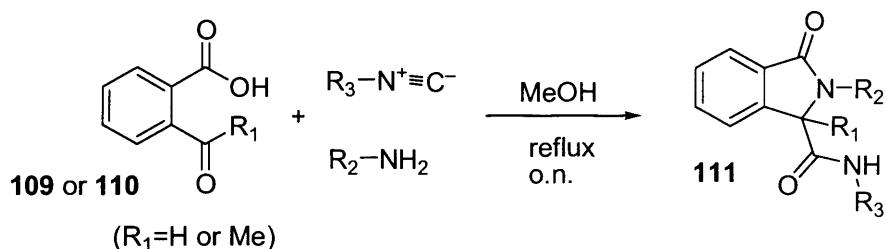
Scheme 45

Harriman suggests a mechanism in which the methanol solvent attacks the mixed imino-anhydride **107** prior to ring closure to the lactam, and this suggestion is substantiated by the fact that the reaction would not operate in the absence of methanol (Scheme 46).⁸⁰



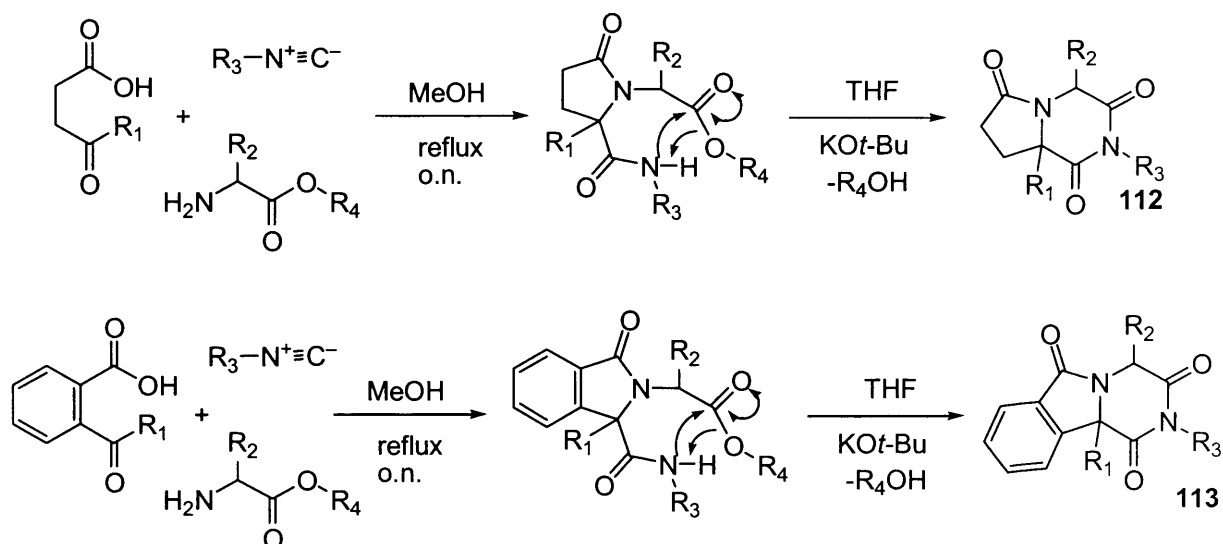
Scheme 46

The use of phthalaldehydic acid **109** and 2-acetyl benzoic acid **110** as carbonyl-carboxylic acid substrates in the Ugi reaction has been shown to give bicyclic γ -lactams **111** (Scheme 47).^{79,81}



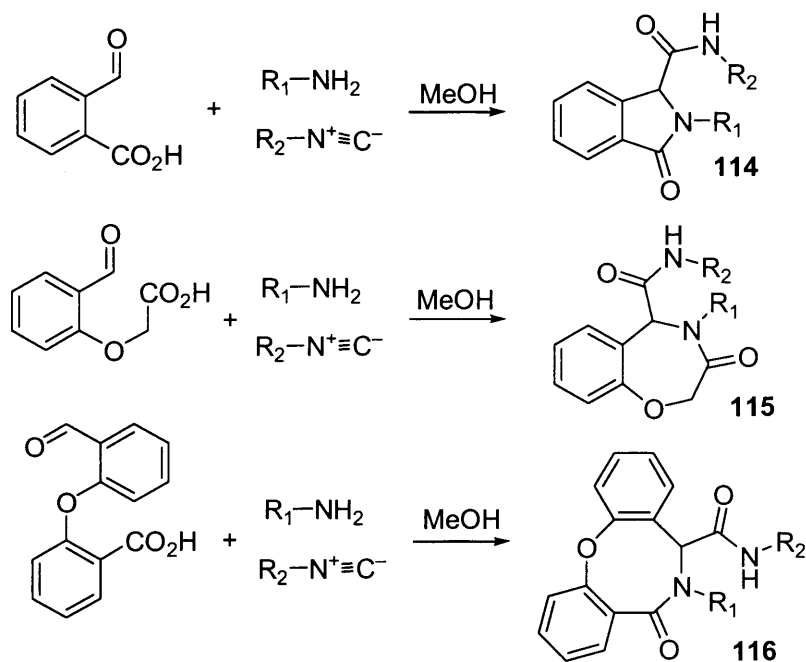
Scheme 47

Hanusch-Kompa and Ugi later applied amino-acid esters to the above reactions furnishing 2,6-piperazinediones **112** and 1,4-diazabicyclo[4,3,0]nonane-3,5,9-triones **113** respectively by the combination of an U-4C-3CR with an intramolecular amide bond formation using potassium *tert*-butoxide in the second step (Scheme 48).⁸¹



Scheme 48

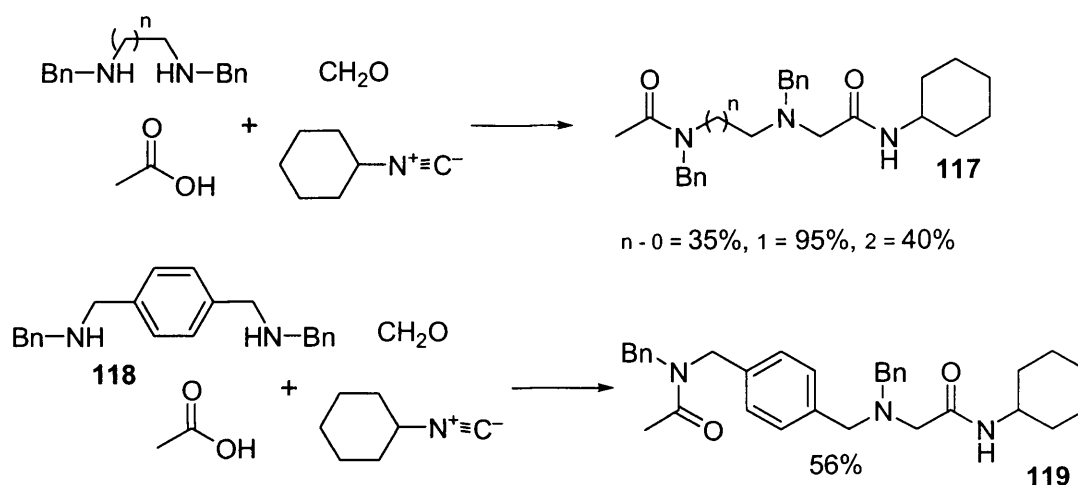
Zhang and co-workers have demonstrated a similar use of suitably tethered aldehyde-carboxylic acid substrates for four-centred, three-component Ugi reactions (U-4C-3CR).⁸² In this case, the variation of tether length between three, five and six bonds results in a diverse series of cyclic amides (Scheme 49).



Scheme 49

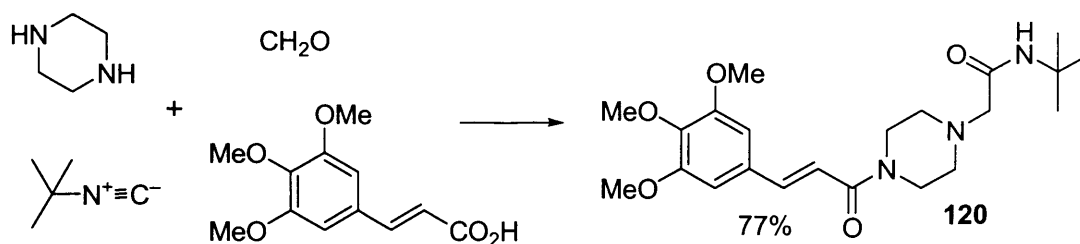
1.524 Diamines as Components in the Ugi Reaction

Giovenzana and Tron recently applied bis-secondary diamines to the Ugi reaction (U-4CR) (Scheme 50).⁸³ Secondary amines are not usually applicable to the standard Ugi reaction since the nitrogen atom of the amino group is unable to take part in the acyl migration step as it is tertiary at this point in the mechanism. One amino group of the diamine is not involved in the initial mechanism between the aldehyde, isocyanide and carboxylic acid, and is thus free to take part in the *N*-acyl migration, producing a novel extended structure to a standard Ugi reaction. Diamines with three through to six bonds separating the amino groups are all shown to be compatible. In the case of diamine **118**, remote transacylation *via* an eleven-membered transition state occurs with a surprisingly high yield of 56%.



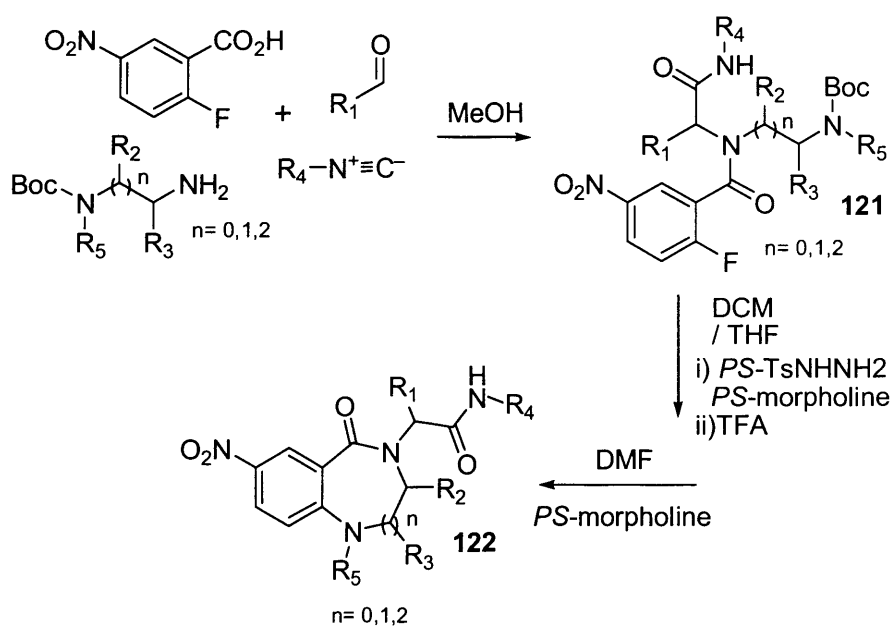
Scheme 50

The synthetic power of this reaction can be exemplified by the one-step synthesis of the known vasodilator **120** (Scheme 51), which had previously only been synthesised in a four step sequence from piperazine.⁸⁴



Scheme 51

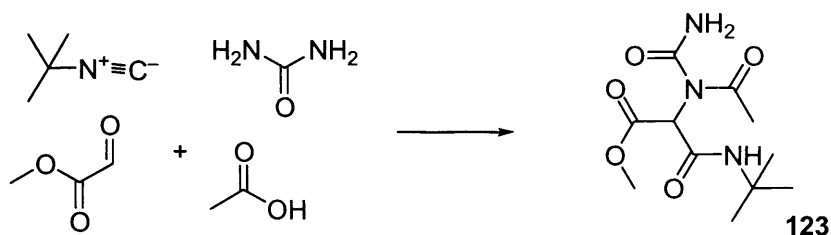
Tempest and Humle have reported the use of singly Boc protected diamines with 2-fluoro-5-nitrobenzoic acid in which the primary amine preferentially forms the imine and takes part in the Ugi reaction leaving a pendant secondary or tertiary amine in the product **121**.⁸⁵ Subsequent treatment with TFA and proton scavenging resins afforded a series of benzazepines **122** by deprotection and $\text{S}_{\text{N}}\text{Ar}$ ring closure (Scheme 52).



Scheme 52

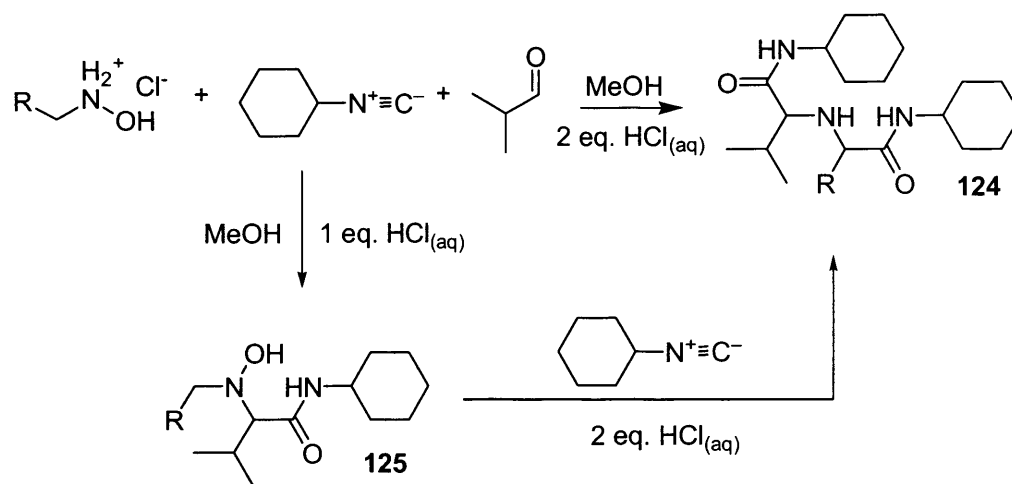
1.53 Alternatives to Amines in the Ugi Reaction.

In 1998, Ugi and Zychlinski demonstrated that urea may be utilised in the place of an amine for the U-4CR (Scheme 53).⁸⁶



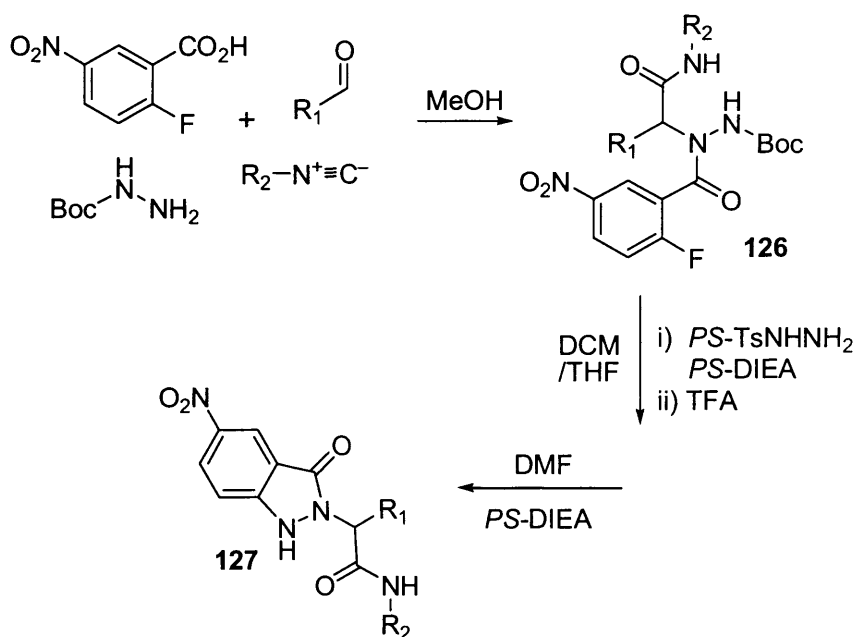
Scheme 53

Moderhack demonstrated the use of hydroxylamines as substrates for an isocyanide based three-component reaction (Scheme 54).⁸⁷ When only 1 equivalent of aqueous protic acid is present, **125** is isolated, however, with 2 equivalents of acid, 2,2'-iminodicarboxdiamide **124** is produced.



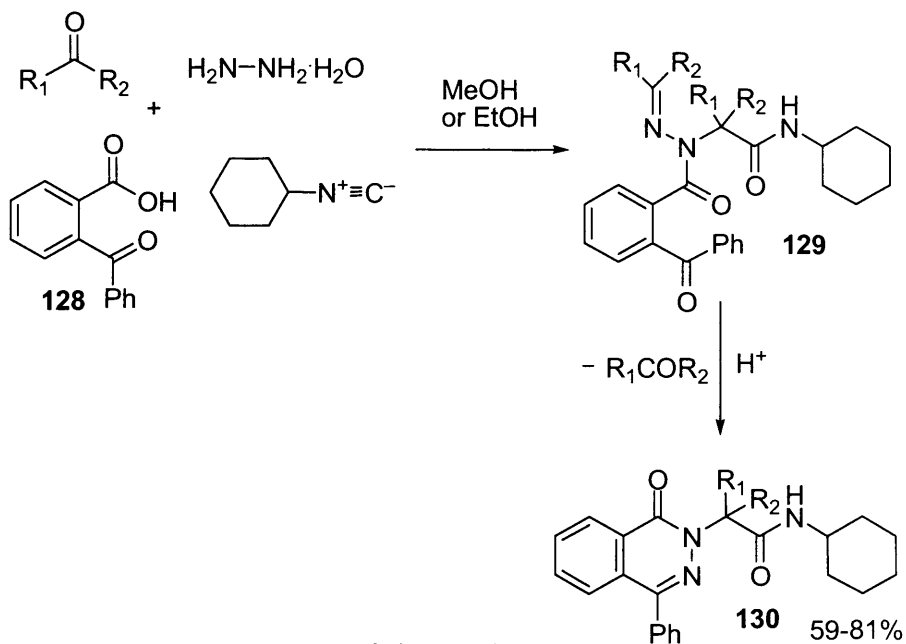
Scheme 54

Tempest *et al.* demonstrated the use of a singly Boc-protected hydrazine in an U-4CR with subsequent $\text{S}_{\text{N}}\text{Ar}$ cyclisation to give dihydroindazol-3-ones **127** (Scheme 55).⁸⁵



Scheme 55

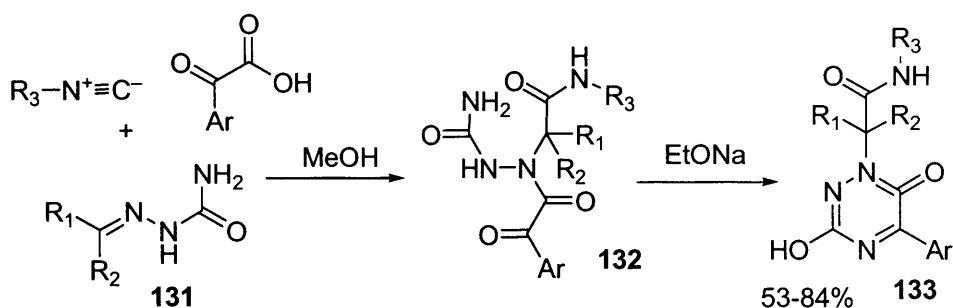
Marcaccini *et al.* have applied hydrazine monohydrate, a carbonyl compound, cyclohexyl isocyanide and 2-benzoyl benzoic acid **128** in a U-4CR via the azine to produce 4-phenyl-1-(2H)-phthalazinone-2-alkanoic acid amides **130** after subsequent acidic workup and loss of one molecule of the initial carbonyl group (Scheme 56).⁸⁸



Scheme 56

Recently, Marcaccini *et al.* have also shown that semicarbazones **131**, react in the place of an amine and carbonyl compound in a U-3CR reaction using benzoyl or 4-

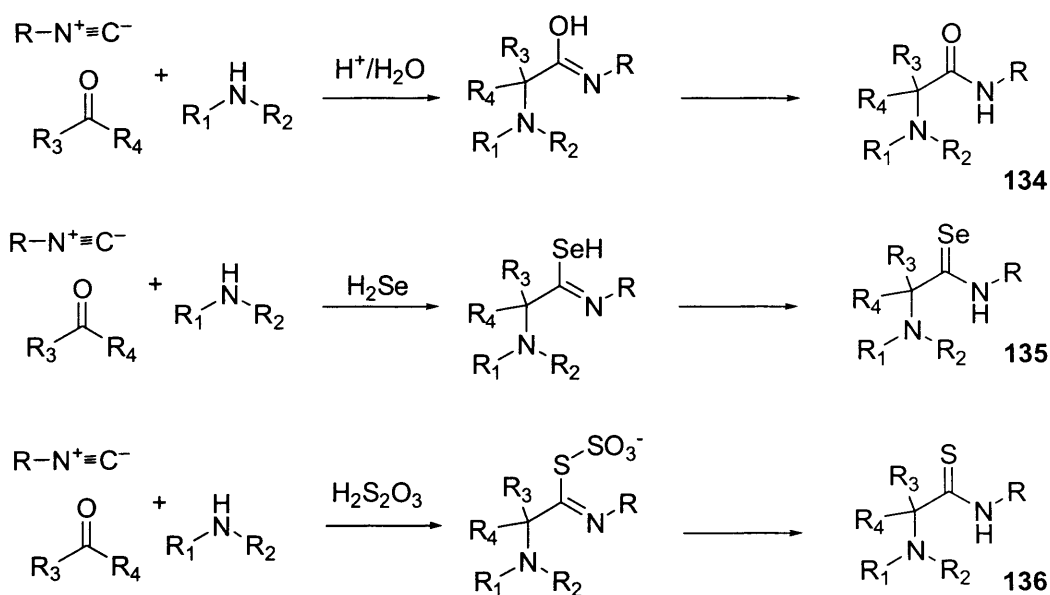
methoxybenzoylformic acid, the adduct of which **132** gives 3-hydroxy-6-oxo[1,2,4]triazin-1-yl alaninamides **133** upon treatment with sodium ethoxide (Scheme 57).⁸⁹



Scheme 57

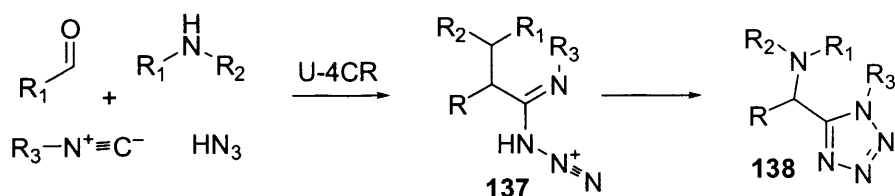
1.54 Alternative Nucleophiles to Carboxylic Acids for the U-4CR.

In the presence of a protic acid, water may act as a nucleophile in the Ugi reaction to produce an α -amino alkylamine **134** (Scheme 58).^{44,58,90} In this case, the α -adduct is stable and no further rearrangement occurs. Similarly, hydrogen selenide⁹¹ and hydrogen thiosulfate,⁹¹ produce stable products with either primary or secondary amines, a carbonyl component and an isocyanide (Scheme 58).



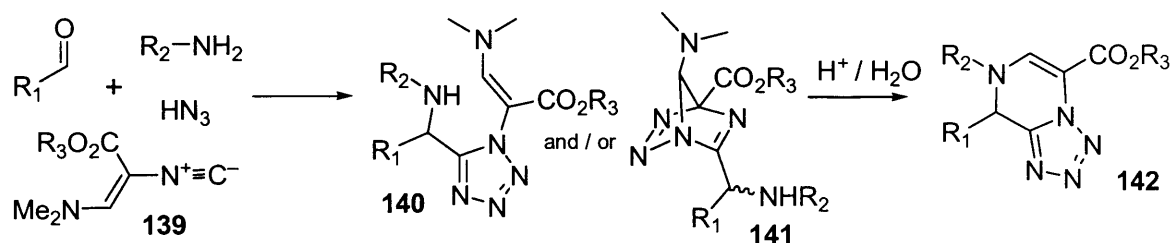
Scheme 58

In 1961, Ugi realised the potential of using hydrazoic acid as the acid component of the Ugi reaction with either primary or secondary amines to produce substituted amino-tetrazoles **138** (Scheme 59).⁹²



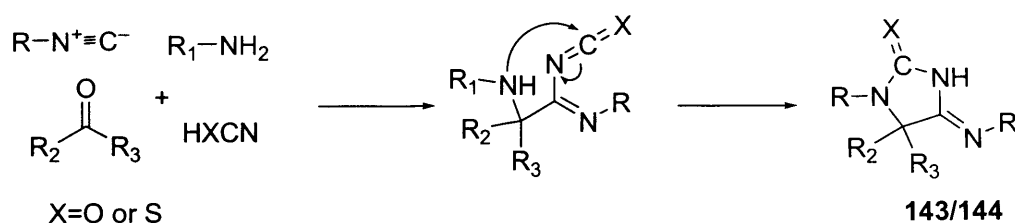
Scheme 59

This methodology has been extended by Bienayme by the use of readily available alkyl- β -(*N,N*)-dimethylamino- α -isocyanoacrylates **139**,⁹³ wherein the initial reaction is followed by acid catalysed cyclisation to produce interesting biologically relevant bicyclic tetrazoles in fair to good yields (Scheme 60).⁹⁴ The often isolated - azanorbornanes **141** - formed by internal azide / olefin [3+2] cycloaddition revert to the standard Ugi product **142** upon treatment with dilute aqueous acid.



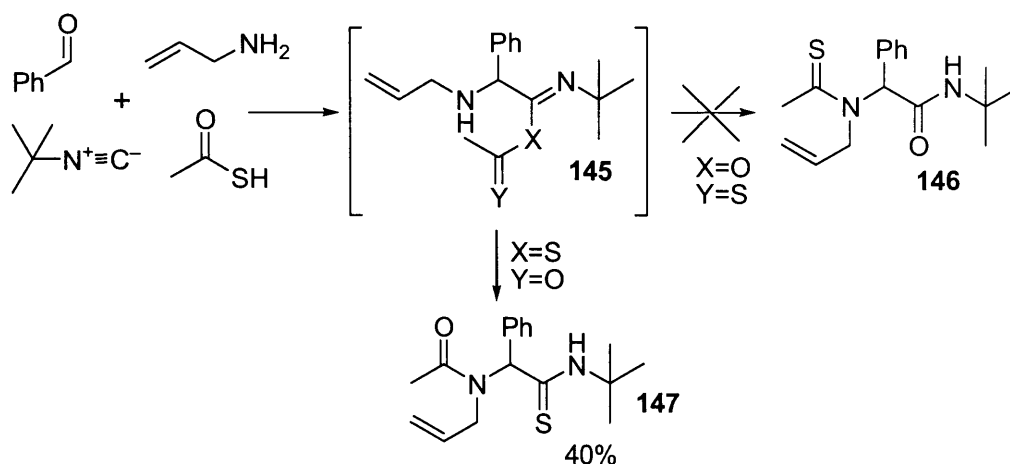
Scheme 60

Hydrogen cyanate⁹⁵ and hydrogen thiocyanate⁹⁶ may be used for the U-4CR in the place of the ubiquitous carboxylic acid to produce hydantoin-4-imides **143** and 2-thiohydantoin-4-imides **144** respectively (Scheme 61). As is the case with a carboxylic acid nucleophile, only a primary amine will react in this manner.



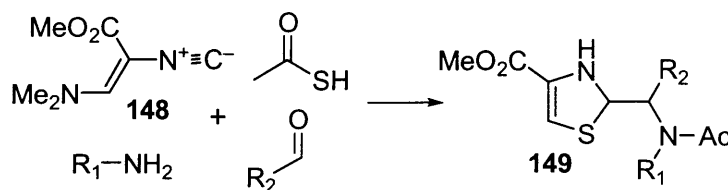
Scheme 61

In 1999, Domling suggested the use of thioacetic acid as a replacement for the carboxylic acid in an U-4CR. This results in entirely regioselective formation of α -aminoacylthioamides **147**, rather than the corresponding α -aminothio-acylamide **146** (Scheme 62).⁹⁷ This is due to the nucleophilic nature of the thioacid which exclusively forms only one structural isomer of intermediate **145**.⁹⁸



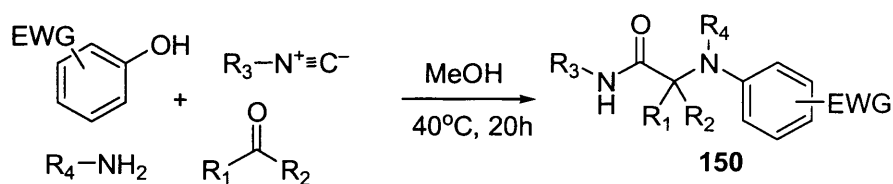
Scheme 62

The combination of a thioacid with Schollkopf's aforementioned β -dimethylamino- α -isocyanoacrylate **148**,⁹³ which has a good leaving group at the β -position has also been explored, and allows the one-pot synthesis of 2,4-disubstituted thiazoles **149**, (Scheme 63).



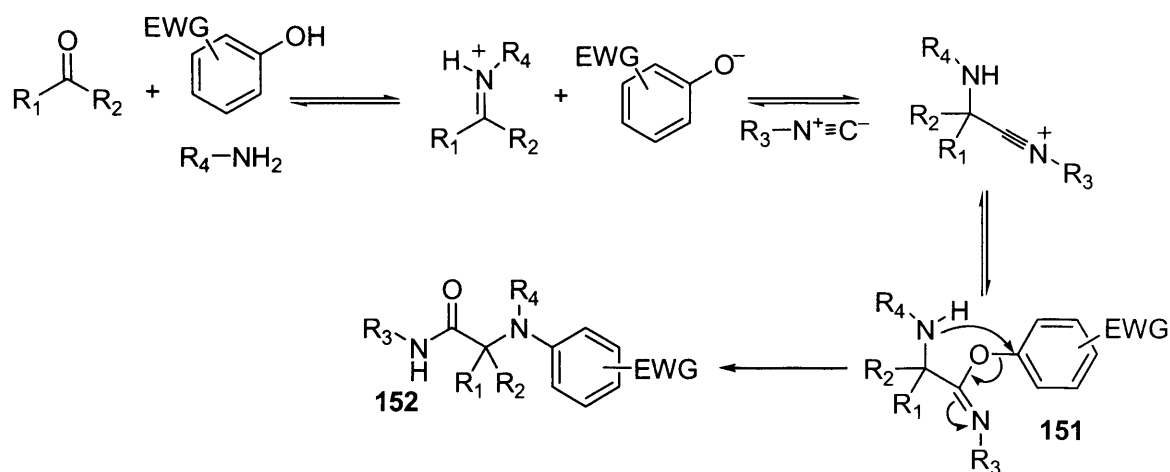
Scheme 63

In conjunction with their abovementioned variant of a Passerini-type reaction using nitrophenols as nucleophiles (*vide supra*, Scheme 18), El Kaim and Grimaud have demonstrated an Ugi-type process which replaces the ubiquitous carboxylic acid with a phenol bearing an electron withdrawing group (EWG) (Scheme 64).⁴⁸



Scheme 64

Protonation of the imine by the acidic phenol leads to an iminium ion which is in turn attacked by the isocyanide in a comparable manner to the classical Ugi reaction. The phenoxide ion is then sufficiently nucleophilic to trap the nitrilium cation forming a labile intermediate **151** which then undergoes a Smiles rearrangement to afford an amino-amide **152** (Scheme 65).⁴⁹



Scheme 65

1.55 Bifunctional Alternative Substrates.

1.551 Tethered Aminoalcohol Substrates

There have been many examples in the literature of the use of ethanolamine as the amine component in the Ugi reaction, in which the hydroxyl group takes no part in the reaction, and *O*-protection is therefore unnecessary.^{99,100,82} Banfi *et al.* have thus carried out a Mitsunobu cyclisation¹⁰¹ using the pendant hydroxyl group in the Ugi product **153** to form diazepanes, diazocanes and dihydrobenzoxapeninones **154** in two steps (Scheme 66).¹⁰⁰



derivatives (Scheme 67).⁸⁵



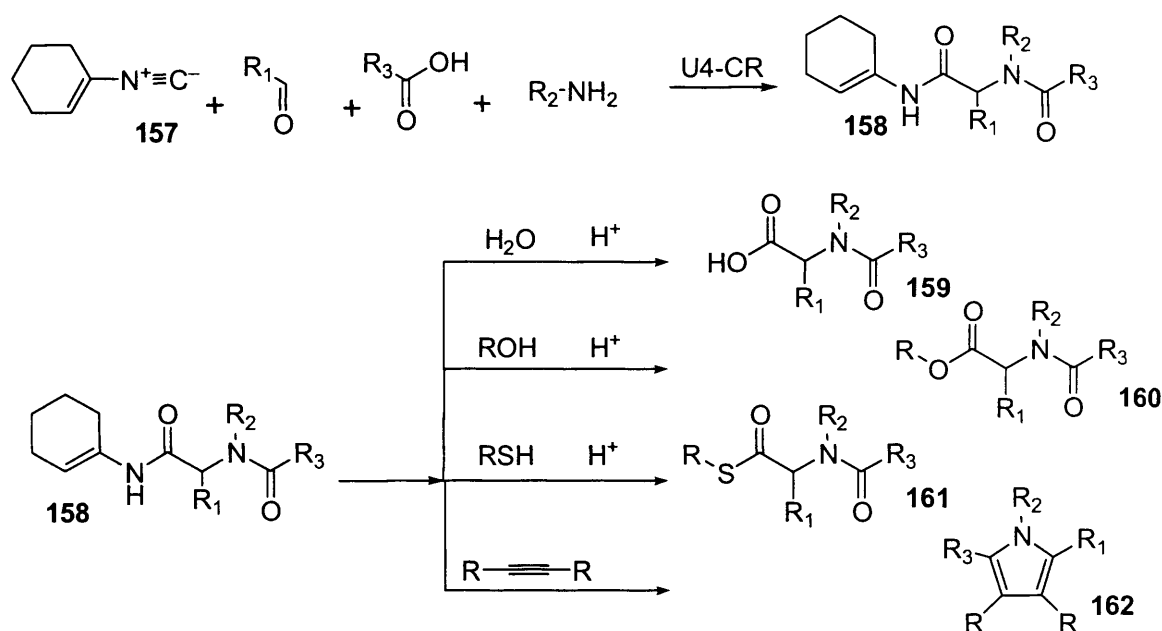
Reactions.

Further diversity may be added to an isocyanide based multicomponent reaction (IMCR) by the use of a substrate which may later be subjected to secondary reactions after incorporation into the IMCR product.¹⁰² This may allow simple diversification of the initial product into a further ‘mini library’ of products including many which

would not be accessible by the initial IMCR step, or allow further synthetic manipulation towards a designated target. This may be achieved by either carrying out MCRs with synthetically labile groups which do not participate in the reaction and thus require protection, or *via* the use of a convertible isocyanide. Some pertinent examples of synthetically labile groups in secondary reactions which are of interest later in this thesis have already been mentioned in the previous section. However, due to the extensive body of work in this area, detailed discussion is beyond the scope of the present introduction.¹⁰³

1.61 Convertible Isocyanides.

Ugi initially published results on the acid cleavable isocyanide, 1-isocyanocyclohexene **157**,¹⁰⁴ and this concept was further developed by Armstrong into the ‘universal isocyanide’ to combat the lack of commercially available isocyanides.¹⁰⁵ The isocyanide component has long been the weak link in the pool of starting materials for the Ugi and Passerini type reactions, with a considerably larger array of the other substrate types commercially available for combinatorial approaches to be carried out. Thus, the ‘universal isocyanide’ (1-isocyanocyclohexene) **157** may take part in a series of acid catalysed reactions to modify the isocyanide-derived area of the final product (Scheme 68). Interestingly, in most cases, the isocyanide carbon is the only atom from the original isocyanide to remain in the product after the secondary reaction. An extremely diverse variety of transformations can now be performed as outlined in (Scheme 68).¹⁰⁵



Scheme 68

Some simple potential products of a simple 3P-CR using the 'universal isocyanide' followed by post MCR acid catalysed reactions.

1.7 Application of Multicomponent Reactions Towards Diversity

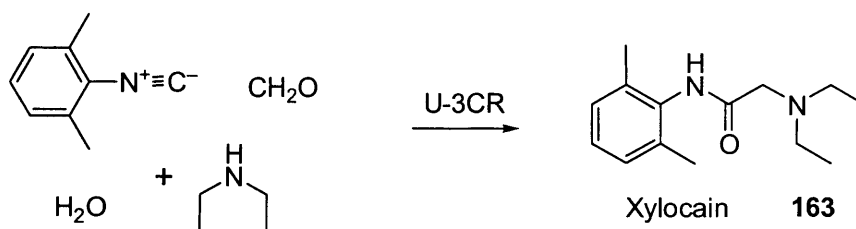
Oriented Synthesis.

Amongst the many advantages of multicomponent reactions (MCRs) are the extremely large numbers of products that may be synthesised from just a small number of starting materials. For example, a three-component reaction (3-CR) using just ten structural permutations of each type of starting material will yield 1,000 different products (10^3) whereas a four-component reaction (4-CR), again using ten structural variants of each will result in 10,000 different products (10^4), all with a similar structural backbone. This range of compounds may be further extended by using the aforementioned method of secondary reactions upon an IMCR product to diversify each product into a further mini-library of compounds.

Recent scientific developments, including genome analysis & proteomics (leading to a plethora of new drug targets) and high throughput automated combinatorial methods (especially those linked to the solid phase) have led to an increased demand

for a greater number of increasingly complex compounds for drug discovery. This may be in part, addressed by the development of novel MCRs, which produce pharmacologically interesting structures.

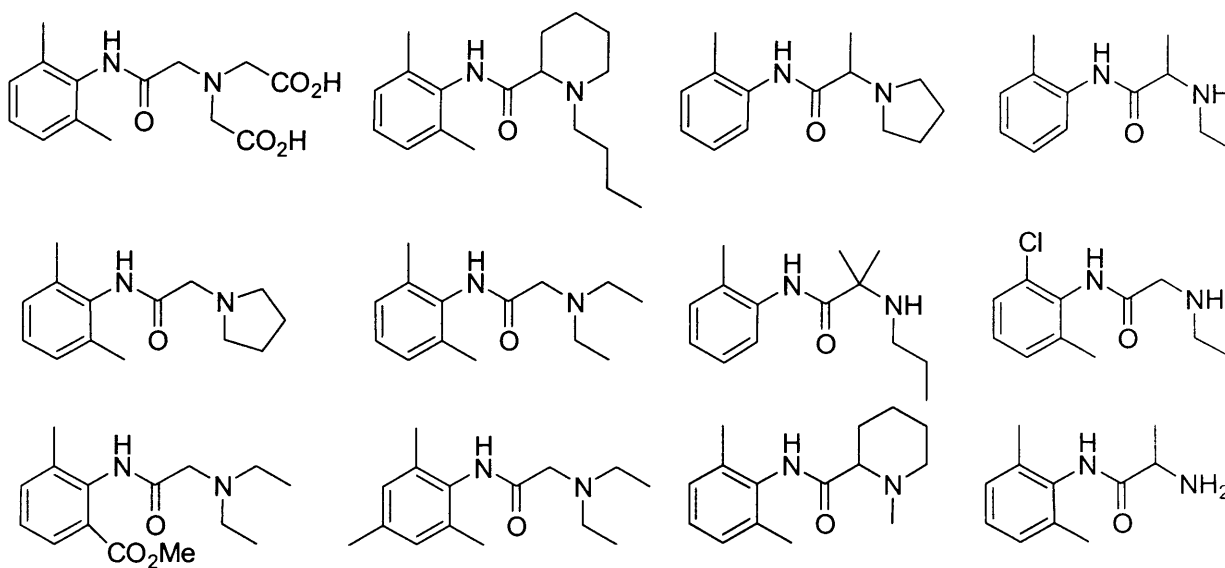
α -Amino-amide based local anaesthetics are an early success story of the targeted library approach to drug discovery, as appropriately demonstrated by the synthesis of the local anaesthetic Xylocain **163** by an U-3CR. This is produced simply from cheap, readily available starting materials in good yield over just one step and provides an excellent example (Scheme 69) ¹⁰⁶



Scheme 69

No fewer than twelve local anaesthetic structures based on this α -amino-amide structure of Xylocain **163** have since been produced and sold globally (Scheme 70).¹

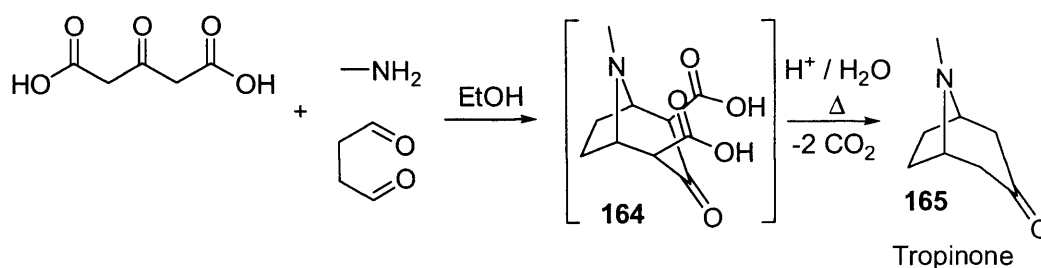
This was the result of Ugi's early foresight into the 'combinatorial type' synthesis of large numbers of structural analogues of a biologically active IMCR product.



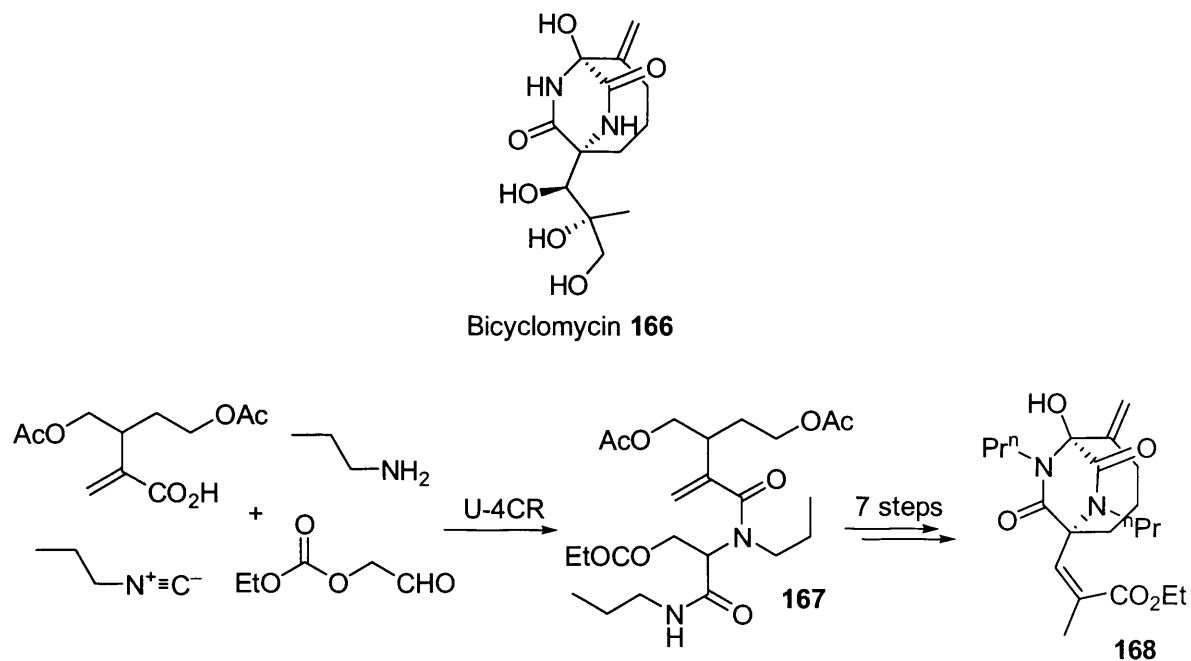
Scheme 70

1.8 Applications of Multicomponent Reactions Toward Target Orientated Synthesis.

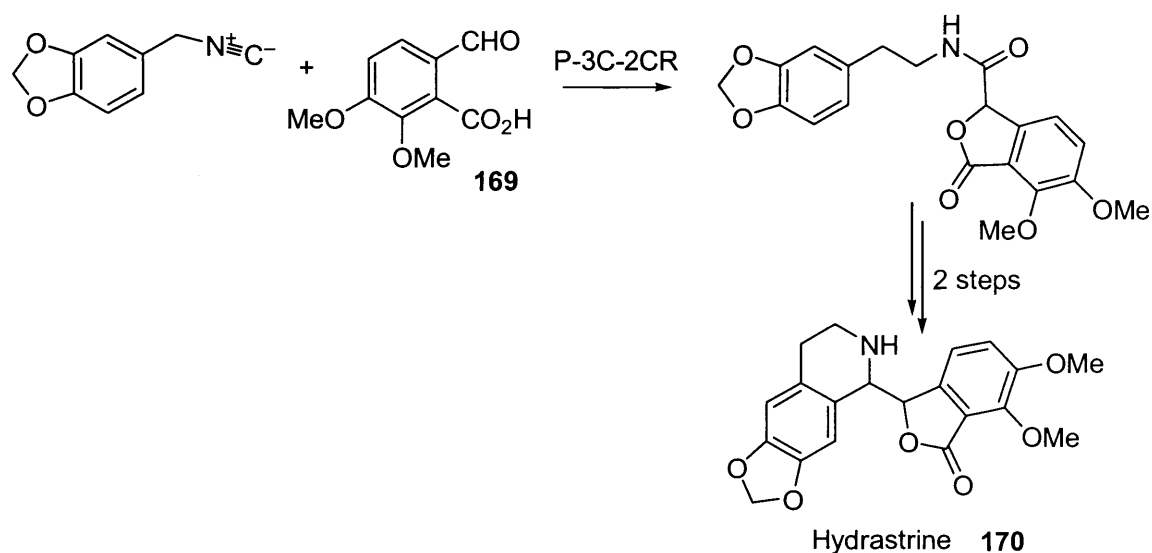
Total syntheses of a target molecule are usually carried out in several reaction steps, with protection and deprotection procedures often required therein. At each stage, the intermediates must be separated and purified to prevent a build up of impurities, before they can be used as an educt of the next step in the sequence. The overall yield of such a stepwise synthesis decreases sharply to a first order approximation with each further required step. Multi-component processes achieve multiple-bond formation in an operationally simple ‘one-pot’ manner; thus potentially allowing the generation of a high degree of complexity from simple, readily available starting materials, and therefore are an ideal tool for target-orientated synthesis. The first and most important example of a MCR in the field of natural product synthesis is, of course, Robinson’s classical synthesis of the alkaloid Tropinone **165** (Scheme 71).¹⁰⁷



Analogues **168** of the complex gram-negative active antibiotic bicyclomycin **166** which is isolated from *streptomyces sapporonensis*¹⁰⁸ were synthesised by Fukuyama in only eight steps using an Ugi-four component condensation (U-4CR), to build in the bulk of the carbon skeleton by the production of four bonds in only one step. (Scheme 72).¹⁰⁹



The intramolecular Passerini reaction with bifunctional α -carboxylic aldehyde **169** allows a three-step synthesis of the alkaloid Hydrastine **170**, once again demonstrating the structural complexity, which may be built up in just one step using a multicomponent reaction (Scheme 73).¹¹⁰



Overview.

The chemistry of IMCRs has not been anywhere near as extensively investigated in the last century as simple two-component chemistry. This is part due to their foul odour as well as the lack of available methods for their synthesis in the first part of the last century. IMCRs therefore still have large unknown areas yet to be discovered. It is important that continued effort is put into discovery of new IMCRs to probe new and exciting structural space as well as the further investigation of existing reactions. The example of the Ugi reaction shows the large amount of mechanistic ambiguity still existing for many IMCRs, mainly due to the greater number of degrees of freedom present in the reaction.

The discovery of new IMCRs may be facilitated by an intelligent design approach, or more often, perhaps in a serendipitous manner. Modern approaches include the use of combinatorial reaction finding techniques,^{111,112} whereby a collection of compounds with a variety of functional groups are reacted in each possible permutation.

In the following chapter we will discuss our own attempts towards the development of a series of novel IMCRs *via* the use of interesting bifunctional starting materials as well as attempts to investigate novel replacements for the ubiquitous carboxylic acid nucleophile therein.

Part 2:

RESULTS and

DISCUSSION

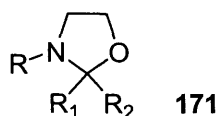
2.1 Introduction.

Since the first part of this work involves the use of 1,3-oxazolidines **171** and their antecedent β -aminoalcohols **174** in a series of novel isocyanide based multicomponent reactions (IMCRs), it is therefore pertinent to briefly introduce this interesting class of saturated *N-O* heterocyclic compound.

2.2 Oxazolidines.

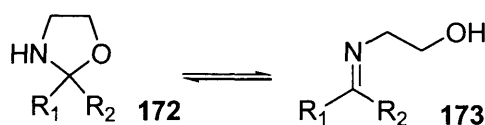
2.21 Structure.

Oxazolidines **171** are saturated five-membered heterocycles of the general structure shown in Scheme 74.¹¹³ They were discovered by Knorr in 1901 by the condensation of a β -aminoalcohol **174** with a carbonyl compound.¹¹⁴



Scheme 74

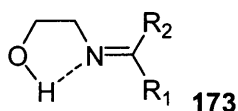
In cases where the nitrogen atom is trisubstituted, the five-membered ring structure has been well established (Scheme 74). However, where $R=H$, a labile tautomeric system is present in which the cyclic oxazolidine **172** may exist in equilibrium with the ring opened – imine tautomer **173** (Scheme 75).



Scheme 75

There has been a great deal of debate and research into the exact nature of these *NH* oxazolidines, and indeed, many exist exclusively as the cyclic structure **172**, whereas others are present entirely as the imine **173**. Infrared spectroscopy, NMR and

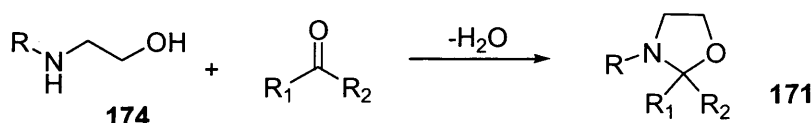
molecular refraction have all been used to ascertain the structure and equilibrium ratios of particular *NH* oxazolidines. What seems certain is that aldehyde derived oxazolidines ($R_1 = H$) tend to favour the cyclic oxazolidine form **172** when $R_2 =$ alkyl, and favour the imine form **173** when $R_2 =$ aryl. This is due to the increased stability of the imine afforded by conjugation with the aryl group. Ketone derived *NH* oxazolidines, in many cases exist as a mixture of both tautomers. Interestingly, infrared spectroscopy results have shown that in almost all cases there is little or no intramolecular hydrogen bonding between the hydroxyl group and imine in tautomer **173** as depicted in Scheme 76.¹¹³



Scheme 76

2.22 Synthesis.

Several methods exist for the synthesis of oxazolidines **171**, but by far the most prevalent is the condensation of a β -aminoalcohol **174** with a suitable carbonyl compound (Scheme 77).



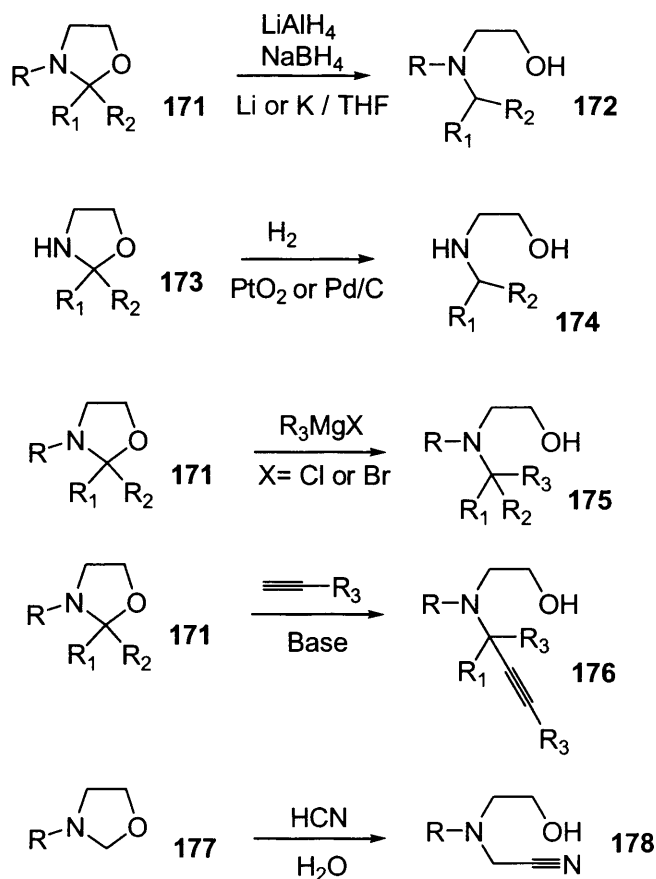
Scheme 77

Many conditions have been applied to this reaction. Solvents including ethanol,¹¹⁵ chloroform,¹¹⁶ toluene,¹¹⁷ benzene¹¹⁸ or diethyl ether¹¹⁶ have been used. Catalysts and additives including iodine,¹¹⁹ acetic acid¹²⁰ and anhydrous potassium carbonate¹¹⁴ have been shown to be successful in reducing reaction times and facilitating the preparation of difficult examples. The most commonly used method involves azeotropic distillation using Dean and Stark conditions.^{118,120} Reaction times vary from almost immediate formation in the case of many aldehydes to 67 hours for the

reaction between 2-amino-2-methyl-1-propanol and butan-2-one.¹¹³ In general however, most examples are complete in under one hour. The relative reactivity of carbonyl compounds with different β -aminoalcohols may be estimated by the measurement of reaction time for complete conversion under azeotropic distillation conditions. Use of aldehydes results in shorter reaction times, due to their increased electrophilicity compared with ketones. Substitution of the nitrogen atom of the β -aminoalcohol **174** has a significant effect on the rate of oxazolidine formation due to both electronic and steric factors. Substitution on the methylene groups and in particular geminal disubstitution of the aminoalcohol has a profound effect on the rate of reaction due to the Thorpe-Ingold effect and analogous steric factors.¹¹³

2.23 Reactivity.

NH and *N*-substituted oxazolidines are prone to nucleophilic attack by a series of reagents leading to a variety of substituted aminoethanols. These reactions give a complementary method to aminolysis of epoxides for the formation of substituted aminoethanols. Reducing agents such as LiAlH_4 ,¹²¹ NaBH_4 ,¹²² and lithium¹²³ or potassium¹²⁴ in THF give an aminoethanol **172**. Cope and Hancock showed that catalytic hydrogenation of *NH* oxazolidines **173** similarly led to the formation of aminoethanols **174**.^{125,126} Oxazolidines readily undergo nucleophilic addition with Grignard reagents,^{126,127} and acetylides likewise attack oxazolidines leading to formation of alkyne substituted aminoalcohols **176**.^{128,129} Aqueous hydrogen cyanide reacts with formaldehyde derived *N*-alkyl oxazolidines **177** to form cyano-substituted aminoethanols **178**.^{130,131,132} (Scheme 78).



Scheme 78

2.3 Results and Discussion.

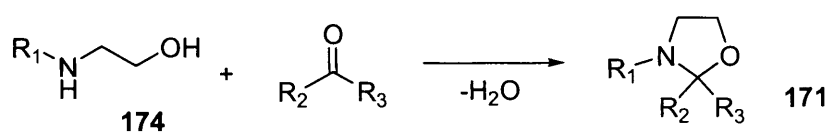
2.31 Preparation of Oxazolidines.

Given the above pattern of reactivity of oxazolidines with nucleophilic reagents, it was of interest to investigate their reactivity with isocyanides, with the objective of exploring the potential of the resultant intermediates in novel isocyanide based multicomponent reactions (IMCRs).

In the first instance, a series of oxazolidines **171** were accordingly prepared by condensation of β -aminoethanols **174** with carbonyl compounds (Scheme 77), the results are summarised in Table 2. Three methods were employed. The first was the traditional method of heating in benzene or toluene under Dean and Stark conditions in the presence of an acid catalyst (Method A). In this case, catalytic *p*TsOH and the

use of a trace of iodine were both found to be equally successful for the reduction of reaction times. A novel second method was developed, wherein repeated concentration of the two reactants from ethanolic solution *in vacuo* led to good yields (Method B). The latter approach was devised with automation of the reaction in mind. When this method was applied to reactions involving aldehydes it resulted in near quantitative conversion to oxazolidines **171** of sufficient purity (by ^1H NMR) for direct use in the IMCRs. Some of the yields quoted in Table 2 are however lower than this due to mechanical loss of material upon small scale distillation.

For the case of volatile carbonyl compounds which could not be employed in the first two methods, a third set of reaction conditions, as developed by Knorr, were used.¹¹⁴ Diethyl ether, at room temperature, in the presence of anhydrous potassium carbonate resulted in good conversion for example **187** (Method C).



R ₁	R ₂	R ₃	Method	Yield 171	Product
<i>p</i> Me-C ₆ H ₄	H	Me	B	90%	179
<i>n</i> -C ₆ H ₁₃	H	Me	A	73% ^a	180
<i>p</i> MeO-C ₆ H ₄	H	Me	B	77% ^a	181
<i>p</i> O ₂ N-C ₆ H ₄	H	Me	B	60% ^a	182
<i>p</i> Me-C ₆ H ₄	H	PhCH ₂	B	97%	183
(CH ₂) ₅		Me	B	86% ^a	184
<i>p</i> Me-C ₆ H ₄	H	^t Bu	A	64% ^a	185
<i>p</i> Me-C ₆ H ₄	H	H	B	89%	186
Me	Me	H	C	80%	187

Table 2. Synthesis of oxazolidines by three methods.

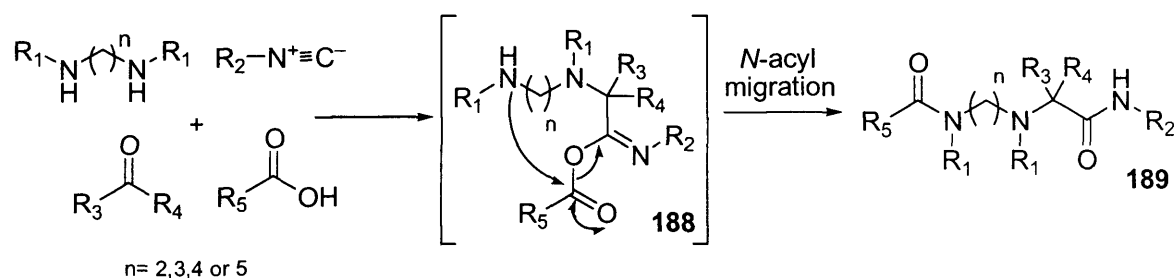
2.32 Three-component Reaction Between an *N*-alkyloxazolidine, Isocyanide and Carboxylic Acid.

With effective methods now in hand for the preparation of the required 1,3-oxazolidines **171**, attention was turned to their use as the electrophilic component in an isocyanide based multicomponent reaction (IMCR).

As previously mentioned (*vide supra*, Schemes 66 & 67), ethanolamine itself has been reported many times as a suitable amine component for the Ugi reaction, in which the hydroxyl group merely acts as a spectator and takes no part in the reaction.

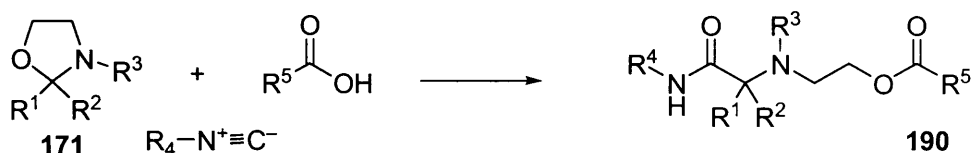
82,99,100

Recently Giovenzana and Tron described the use of bis-secondary diamines in the Ugi reaction (U-4CR) (Scheme 79).⁸³ In this case, one amino group of the diamine is not involved in the initial mechanism between the aldehyde, isocyanide and carboxylic acid, and is free to take part in the ensuing *N*-acyl migration. This reaction results in good to moderate yields despite the extended entropically disfavoured and transannularly strained *N*-acyl migration in intermediates **188** when up to eleven-membered rings are involved (Scheme 79).⁸³



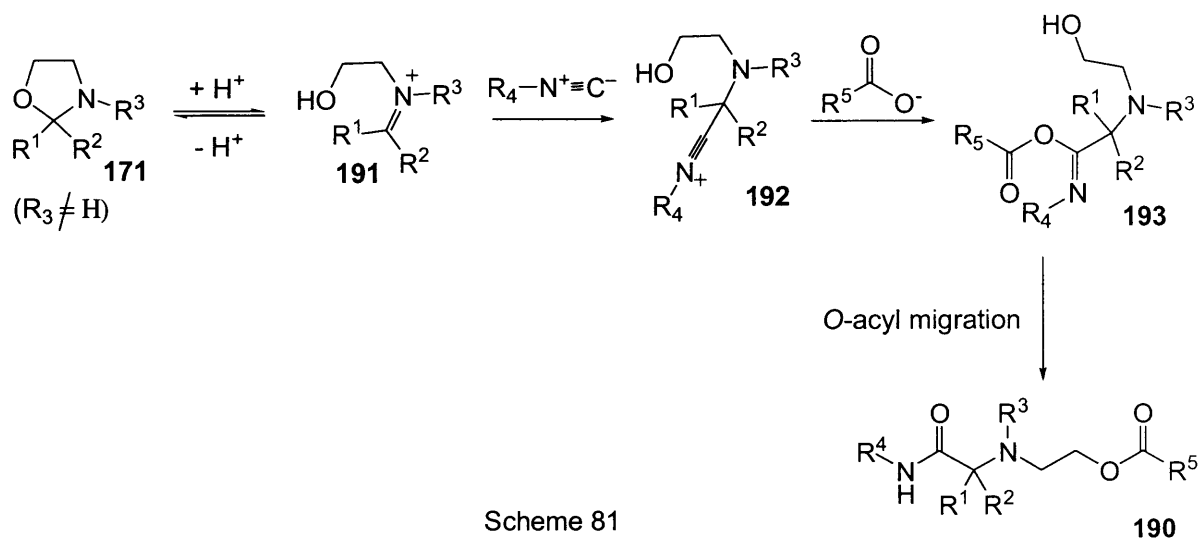
Scheme 79

It was envisaged that by using *N*-substituted ethanolamines to form oxazolidines **171**, a similar reaction with an isocyanide and carboxylic acid could occur (Scheme 80).



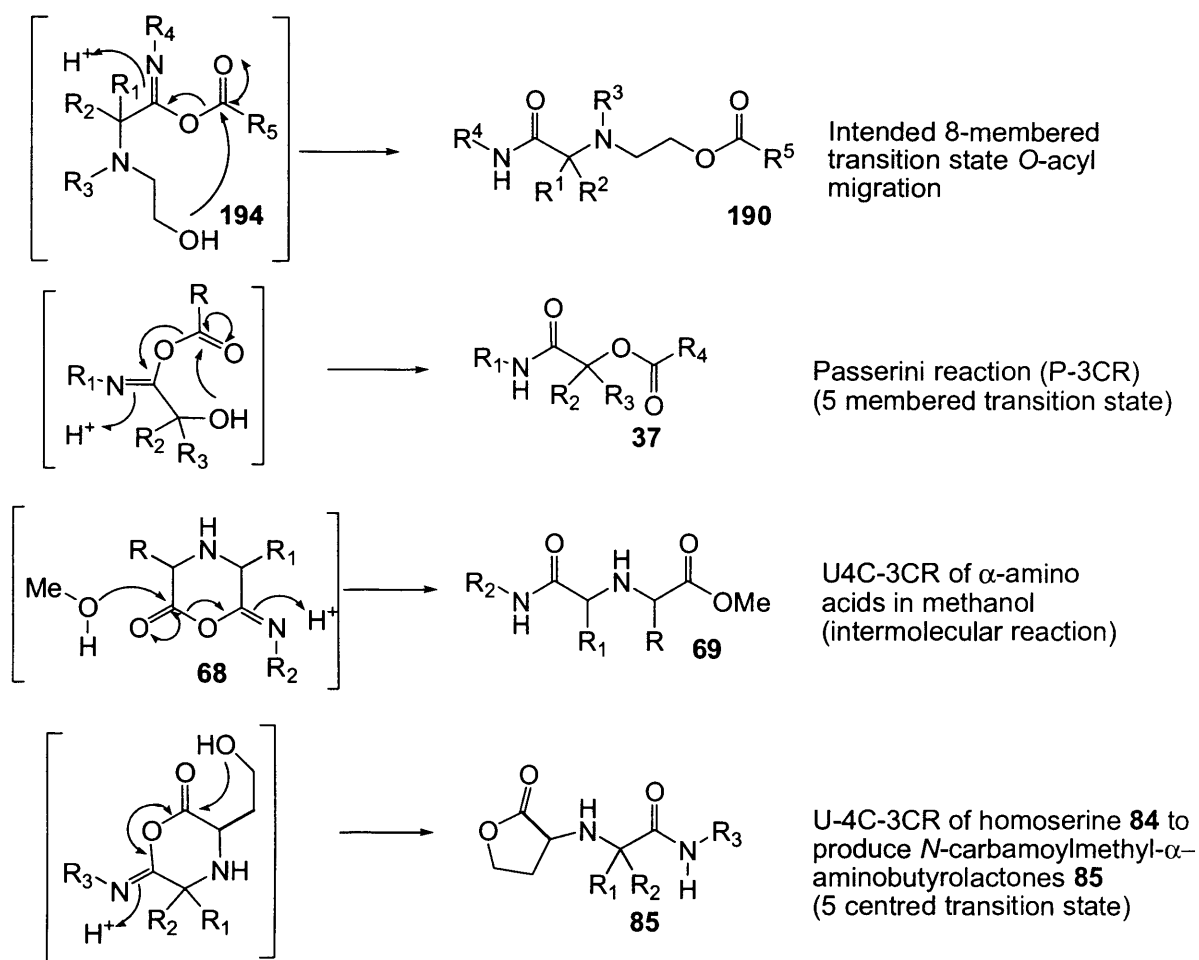
Scheme 80

An initially proposed mechanism for this reaction would involve ring opening of the oxazolidine **171** in the presence of a protic acid to give an iminium ion **191**, which is the reactive electrophilic partner in Ugi type reactions. This would be expected to react in quasi-irreversible fashion with an isocyanide. The resultant nitrilium cation **192** could then be trapped by the carboxylate anion resulting in intermediate **193** (Scheme 81). The use of a secondary *N*-substituted β -aminoalcohol as the amine component should, in this case, eradicate the *N*-acyl migration pathway seen in the Ugi reaction, since the amino group derived from the oxazolidine component in intermediate **193** is tertiary (Scheme 81).



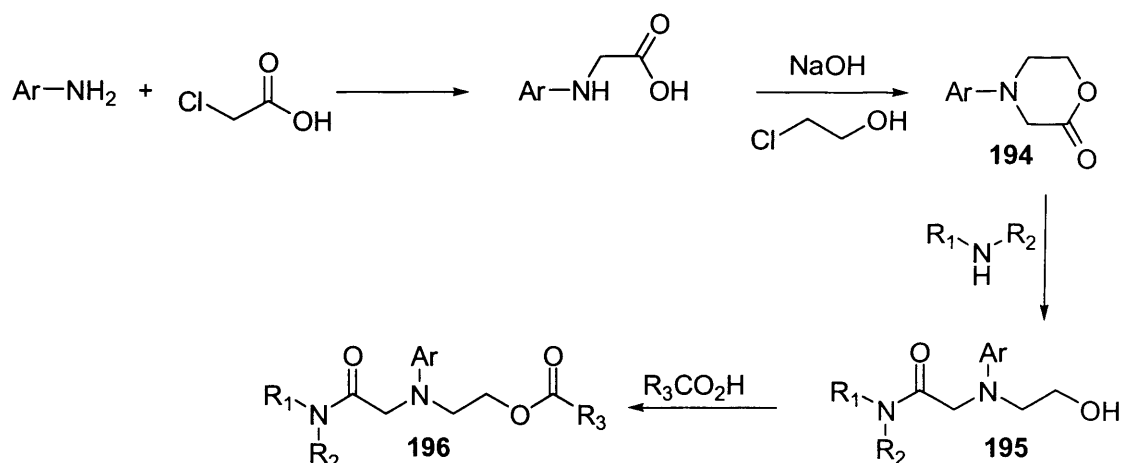
Scheme 81

The anticipated *O*-acyl migration (Scheme 81) benefits from the same thermodynamic driving forces involved in the Passerini reaction,¹¹ the Ugi reaction of α -amino acids in methanol,⁶³⁻⁶⁶ and the Ugi reaction of homoserine **84**,⁷⁰ although, in this case it reacts *via* a larger - eight-membered transition state **194**, and is therefore more entropically disfavoured than the other processes shown in Scheme 82.



Scheme 82

Only one literature precedent for the formation of this class of interesting *N*-acyloxyethylamino acid amide **190** was found in a patent published by Ciba-Geigy[®] for the preparation of such aryl substituted amines **196** as intermediates for azo-dyestuffs (Scheme 83).¹³³

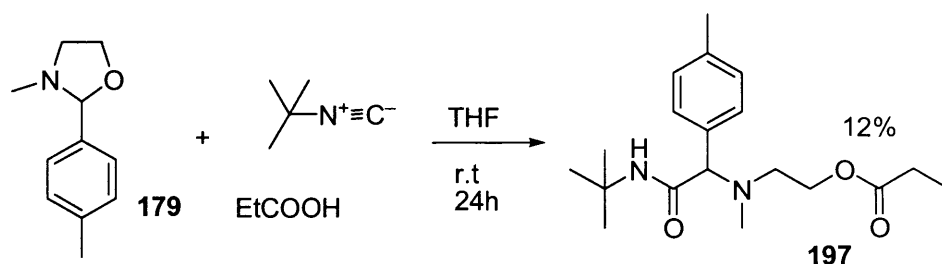


Scheme 83

The proposed 3-CR reaction of an *N*-alkyl oxazolidine, isocyanide and carboxylic acid (Scheme 80) would therefore provide a one-step, highly convergent synthesis of the *N*-acyloxyethylamino acid amide **190** unit in a far simpler and shorter route to that of Ciba-Geigy[®], thereby exemplifying many of the advantages of multicomponent reactions over stepwise reaction sequences. Moreover, this structure was considered to be ideal for compound library synthesis due to the large number of substitutable positions in the various reagents, thereby allowing the preparation of a large variety of examples with the *N*-acyloxyethylamino acid amide core unit **190**.

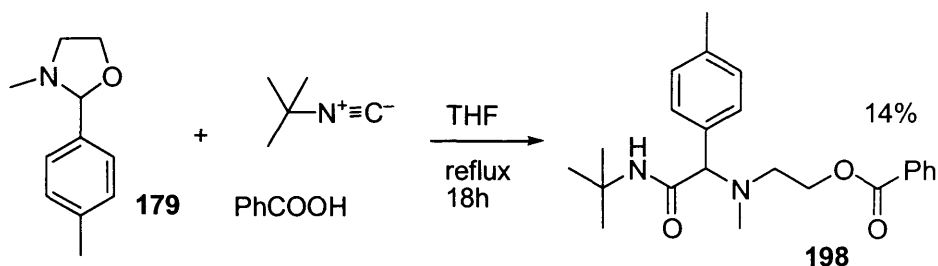
2.33 Initial IMCRs Involving N-alkyloxazolidines.

Gratifyingly, an initial reaction using 3-methyl-2-*p*-tolyl-oxazolidine **179**, *tert*-butyl isocyanide and propionic acid in THF at room temperature was successful, albeit in a disappointing 12% isolated yield (Scheme 84).



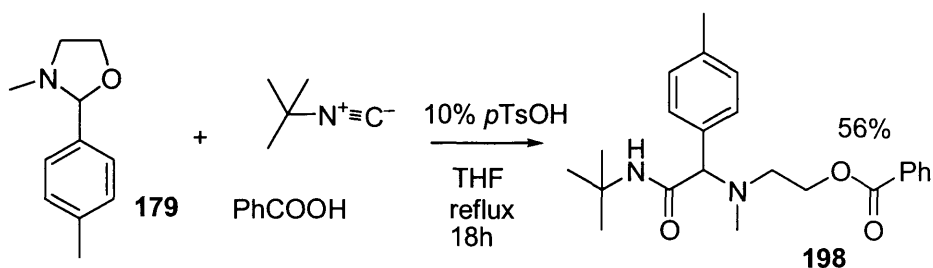
Scheme 84

Increasing the temperature of the reaction to reflux gave no significant improvement in yield for a similar example **198** (Scheme 85).



Scheme 85

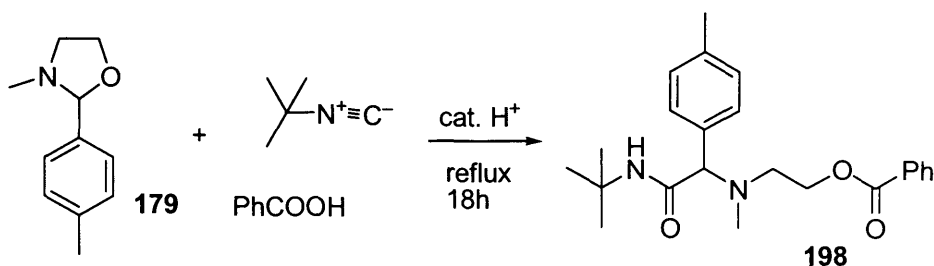
It was therefore considered that the addition of an acid catalyst possessing a non-nucleophilic counterion might increase the rate of reaction by facilitating ring opening of the oxazolidine to the iminium ion. Use of 10 mol% *p*TsOH as an acid catalyst at reflux in THF led to a vast improvement in yield of **198** from 14% to 56% (Scheme 86).



Scheme 86

At this stage, due to the success of *p*TsOH as an acid catalyst, Dowex[®] 50W X4 acidic resin was trialled with a selection of solvents in an initial attempt to optimise the reaction conditions (Scheme 87). Dowex[®] 50W X4 was initially thought to be a good choice of acidic catalyst over *p*TsOH for the screening experiments on practical grounds since it could be removed simply by gravity filtration. Table 3 shows the results of this solvent screen. Only solvents that gave appreciable yields of the desired product are shown and use of acetonitrile was clearly shown to be beneficial. When the superior solvent choice – acetonitrile was used, but this time reverting to the use of 10 mol% *p*TsOH as a homogeneous catalyst instead of Dowex[®] 50W X4

resin, an improved yield of 66% was achieved. These reaction conditions were therefore selected to start investigating the generality of this reaction.



Scheme 87

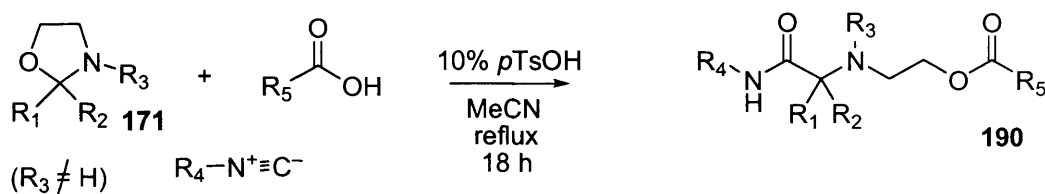
Catalyst	Solvent	Conditions	Yield 198
Dowex	THF	Reflux 17h	24%
Dowex	MeOH	Reflux 17h	30%
Dowex	DMF	Reflux 17h	19%
Dowex	EtOAc	Reflux 17h	38%
Dowex	MeCN	Reflux 17h	52%
<i>p</i> TsOH	MeCN	Reflux 24h	66%

Table 3. Solvent and acid screen for Scheme 87.

2.34 Examples of 3-CR Using *N*-alkyloxazolidines, Isocyanides and Carboxylic Acids under Initially Optimised Conditions.

With these conditions in hand, a variety of *N*-alkyloxazolidines, isocyanides and carboxylic acids, (Scheme 88) were then reacted to yield a selection of *N*-acyloxyethylamino acid amides **190**. As shown in Scheme 88 and Table 4, this reaction tolerates both aliphatic and aromatic isocyanides, but with higher yields seen for aliphatic examples. This is important since many published IMCRs only work well with either one or the other. This reaction also allows the use of aromatic and aliphatic carboxylic acids with no significant difference in yield. The use of the bifunctional and bulky 3-indole propionic acid however, unsurprisingly led to lower yields. Both aliphatic and aromatic aldehyde derived oxazolidines were successful substrates for this reaction, with aliphatic oxazolidine **180** giving the greatest yield. The lower yield for the *para*-nitrobenzaldehyde derived oxazolidine **182**, when

compared with other more electron rich aldehyde derived oxazolidines may only be due to stability issues, rather than inherent electronic factors, since oxazolidine **182** was not stable to storage at room temperature. Ketone derived oxazolidine **184** showed a reasonable yield, similar to those for aromatic aldehyde derived oxazolidines. The large bulky *tert*-butyl substituent on the oxazolidine nitrogen of **185** appeared to have an extremely detrimental effect on the isolated yield.



Scheme 88

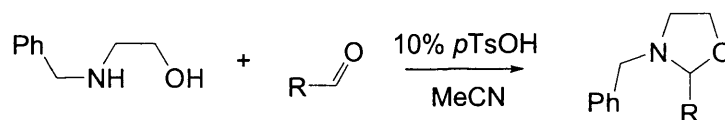
171	R ₁	R ₂	R ₃	R ₄	R ₅	Yield	Product
179	<i>p</i> Me-C ₆ H ₄	H	Me	^t Bu	Ph	66%	197
179	<i>p</i> Me-C ₆ H ₄	H	Me	^t Bu	Et	64%	198
179	<i>p</i> Me-C ₆ H ₄	H	Me	^c C ₆ H ₁₁	Ph	71%	199
179	<i>p</i> Me-C ₆ H ₄	H	Me	ⁱ Pr	Ph	73%	200
180	<i>n</i> -C ₆ H ₁₃	H	Me	^t Bu	Ph	80%	201
180	<i>n</i> -C ₆ H ₁₃	H	Me	^t Bu	Et	78%	202
180	<i>n</i> -C ₆ H ₁₃	H	Me	^c C ₆ H ₁₁	Ph	48%	203
180	<i>n</i> -C ₆ H ₁₃	H	Me	^t Bu	2-(3-indole)ethyl	44%	204
180	<i>n</i> -C ₆ H ₁₃	H	Me	2,6-dimethylphenyl	Et	42%	205
180	<i>n</i> -C ₆ H ₁₃	H	Me	2-methyl-6-chlorophenyl	Ph	29%	206
181	<i>p</i> MeO-C ₆ H ₄	H	Me	^t Bu	Ph	68%	207
182	<i>p</i> O ₂ N-C ₆ H ₄	H	Me	^t Bu	Ph	47%	208
183	<i>p</i> Me-C ₆ H ₄	H	PhCH ₂	^t Bu	Ph	44%	209
184	(CH ₂) ₅		Me	^t Bu	Ph	63%	210
185	<i>p</i> Me-C ₆ H ₄	H	^t Bu	^t Bu	Me	20%	211

Table 4. Results for 3-CR formation of *N*-acyloxyaminoacid amides **190**.

2.35 Four-Component Reaction (4-CR) Using β -Aminoethanols,

Isocyanides, Carbonyl Compounds & Carboxylic Acids with no Prior Condensation.

After the successful three-component reaction (3-CR) for a variety of substrates, (Scheme 88), it was reasoned that an *in-situ* preparation of an *N*-alkyloxazolidine in the presence of the isocyanide and carboxylic acid – a four-component reaction (4-CR) should also be successful. A brief study of the rate of *N*-alkyloxazolidine formation was carried out. Yields were determined by HPLC peak area against a 1,1,1-trifluorotoluene internal standard which had been calibrated against the respective isolated products. Under the previously applied reaction conditions of 10 mol% *p*TsOH in MeCN at reflux the aliphatic aldehyde *n*-heptanal reacted more quickly than the aromatic aldehyde *p*-tolualdehyde, but, in both cases, oxazolidine formation was virtually complete within 30 minutes (Scheme 89, Table 5).



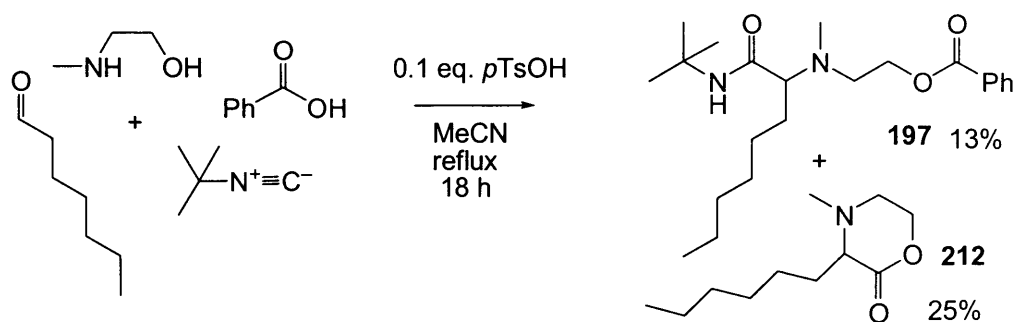
Scheme 89

Time (mins)	R= <i>n</i> -hexyl	R= <i>p</i> -tolyl
2	67%	56%
4	73%	62%
10	85%	76%
30	91%	90%

Table 5. Yields for Scheme 89 at time intervals.

In fact, complete formation of the 1,3-oxazolidine ring is not actually required for the 4-CR to take place provided that the initial imine formation has occurred. Since fast initial imine formation is the first step in a vast multitude of MCRs this was not expected to be problematic. Thus, the required 4-CR was expected to be feasible under the currently optimised conditions.

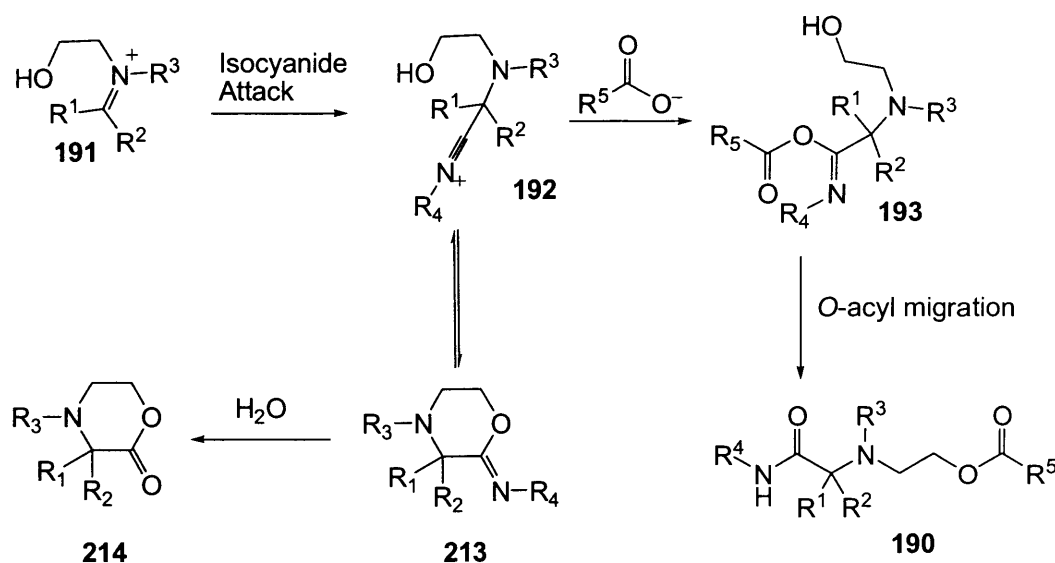
Surprisingly, the reaction between *n*-heptanal, *N*-methylaminoethanol, *tert*-butyl isocyanide and benzoic acid gave a disappointing 13 % yield of the desired four-component product **197** after 18 hours, whilst “morpholinone” **212** was isolated as the major product (25 %) (Scheme 90). The 13% yield of **197** is very low when compared with the 80% yield previously seen when the reaction is carried out in a three-component manner from the oxazolidine **179**.



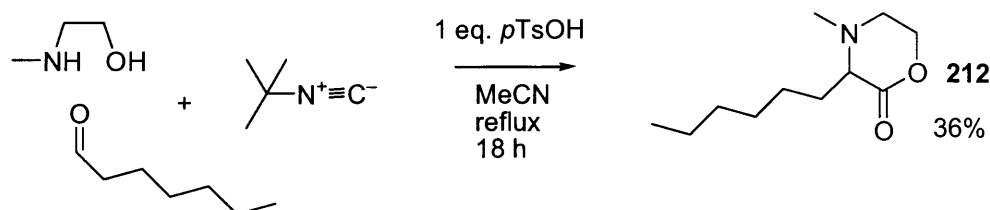
Scheme 90

The formation of **212** suggests the presence of an exocyclic imino ether intermediate **213** in the reaction mechanism (Scheme 91). This intermediate may undergo hydrolysis by water *in-situ* to give the morpholinone derivative **212**. Closer examination of the ^1H NMR spectra of the earlier three-component reactions (*vide supra*) indicated that small quantities of such morpholinone products were also present in the crude reaction mixtures, presumably due to traces of adventitious water in the reaction medium.

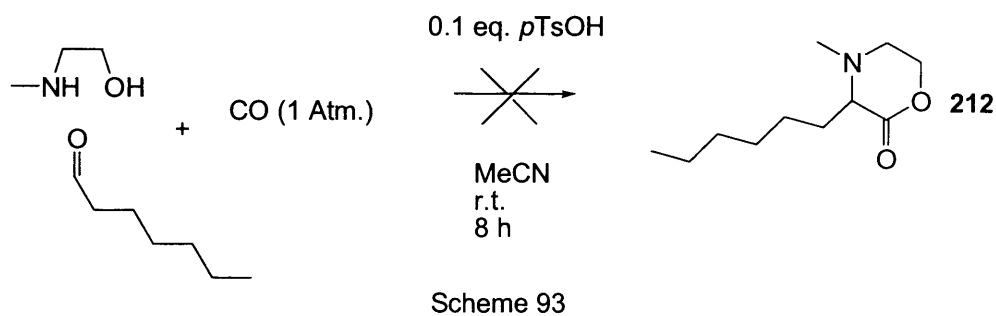
Nucleophilic attack of a carboxylic acid on the nitrilium cation intermediate **192** would lead to the multicomponent product **190** after rearrangement, whereas hydrolysis of the cyclic intermediate **213** would result in the morpholinone product **214** being formed. Therefore, the 4-CR would be expected to lead to formation of significant levels of morpholinone **214**, as compared with the equivalent 3-CR, due to the generation of one equivalent of water during the initial oxazolidine formation.



Some support for this rationale came from an experiment where the reaction between *n*-heptanal, *N*-methylaminoethanol and *tert*-butyl isocyanide was carried out in the absence of a carboxylic acid, but instead with one equivalent of *p*TsOH. In this instance, morpholinone **212** was obtained in 36% yield (Scheme 92).



Due to this disappointingly low yield of the direct morpholinone **212** synthesis, carbon monoxide was applied to this reaction in the place of *tert*-butyl isocyanide (Scheme 93). Carbon monoxide is isoelectronic with an isocyanide (*vide supra*, Figure 1), and so was thought to be an ideal and more atom economical alternative to *tert*-butyl isocyanide for this C=O insertion reaction. Sadly, after 8 hours, no reaction was detected by TLC or ^1H NMR.



The low yield of morpholinone **212** from the reaction between *n*-heptanal, *N*-methylaminoethanol and *tert*-butyl isocyanide (Scheme 92) led to the use of a more modern method for the planning of experiments and subsequent statistical analysis of the results - a Design of Experiments (DoE) or Factorial Experimental Design process.¹³⁴ It is therefore appropriate at this stage to briefly introduce this powerful statistical tool and its applications within organic chemistry.

2.4 Introduction to the Design of Experiments (DoE) Approach in Organic Synthesis.

Design of experiments (DoE) is a method of planning experiments prior to their being realised in order to allow analysis of the data by multivariate statistical techniques.

DoE originated in 1925 with the initial research of Fisher.¹³⁵ Over the last few years this method, which has previously seen most use in the industrial sector, has seen increasing use by academic chemists.

2.41 One Variable at a Time Experimental Method.

When a series of experiments, for example optimisation of a new chemical process is carried out it is common to adopt an iterative, one variable at a time (OVAT) approach. This is the seductively simple and seemingly successful, classical method of chemical experimental planning and allows the experimentalist to ensure beyond doubt that any effect *e.g.* a change in yield is due to the change in variable they have just effected. However this method is a poor strategy, which may lead to the wrong

conclusions. For instance, in the case of a yield optimisation for a reaction with two variables, OVAT methods would lead the experimenter to change one variable initially until a maximum yield is achieved for this variable. Then the second variable would be investigated with the first variable fixed at the new optimised level. This overly simplistic method can lead to incorrect conclusions if there is an interaction between the two variables, since the actual optimised yield may not in fact have been discovered. It also teaches the researcher nothing about any interaction present and can also be inefficient and time consuming.

2.42 Considerations Prior to Construction of an Experimental Design.

Experiments run in a random manner will furnish results in an arbitrary fashion. For this reason, it is therefore necessary to plan a series of experiments prior to their being carried out if detailed information is to be gained from the resultant data. It is essential to state clear objectives prior to the construction of an experimental design. These objectives may for example be to determine optimum reaction conditions, or perhaps to ascertain if a change in a particular reaction condition will have a significant effect upon yield or selectivity. However, it is sensible to produce an experimental design only after some initial results and experience of the reaction system has already been gained. This will ensure that the reaction will give a measurable response and also assist in deciding which parameters require investigation.

In recent years a plethora of DoE computer software programs have become available, which allow the statistical planning of experiments and interpretation of the results in a simple user friendly graphical manner. Nevertheless, it is still important to understand the basic mathematical principles behind the software. The next

section will briefly introduce the concepts which are integral to the whole practice of DoE.

2.43 Response Surface Models as Tools for the Chemist

A graph showing two experimental factors (x_1) and (x_2) against a given response (μ), will give a three-dimensional plot (Figure 2). This is a graphical representation of a reaction surface. This is simple to visualise when there are only two variables and one measured response, but when there are multiple variables and / or responses it is not possible to graphically represent a multidimensional plot, however, the concepts involved remain the same.

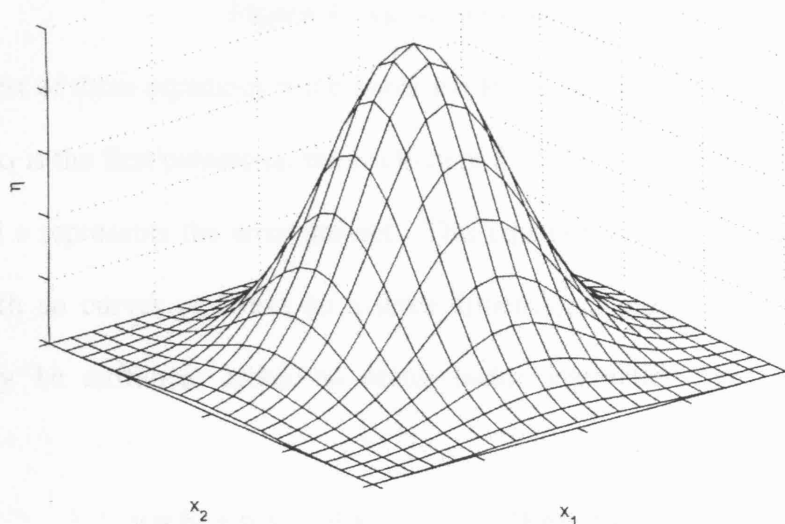


Figure 2. (reproduced from ¹³⁴).

The surface of an experimental domain may be described by a complex equation called the Taylor expansion.¹³⁶ Fortunately, sufficiently accurate modelling of this experimental domain surface is simple, since the chemist is not usually looking at the entire range from $0-\infty$ for each variable, but, instead, often only a narrow range. For instance, with reaction temperature, the area of interest is often only 0°C to the solvent boiling point. Therefore only the relevant section of the experimental domain

needs to be modelled (Figure 3) and to do this, one of three polynomial equations may be employed.

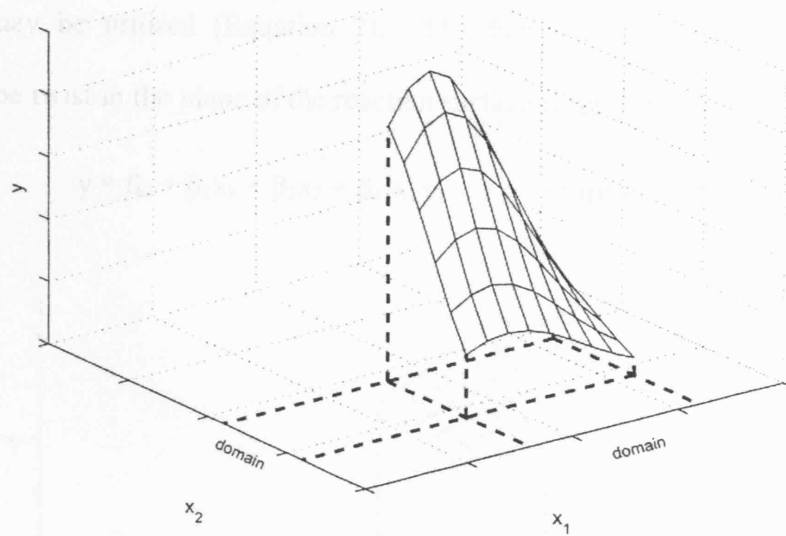


Figure 3. (reproduced from¹³⁴).

The simplest of these equations is the linear model or 1st order polynomial (Equation 1), where x_1 is the first parameter, the coefficient β_1 is the slope of the plane along the x_1 axis and e represents the error present. This equation may be thought of as a flat surface with no curves or twists on a three dimensional plot (Figure 4). A linear model may be sufficient when no factor-factor interactions are needed to be modelled.

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + e \quad \text{(Equation 1).}$$

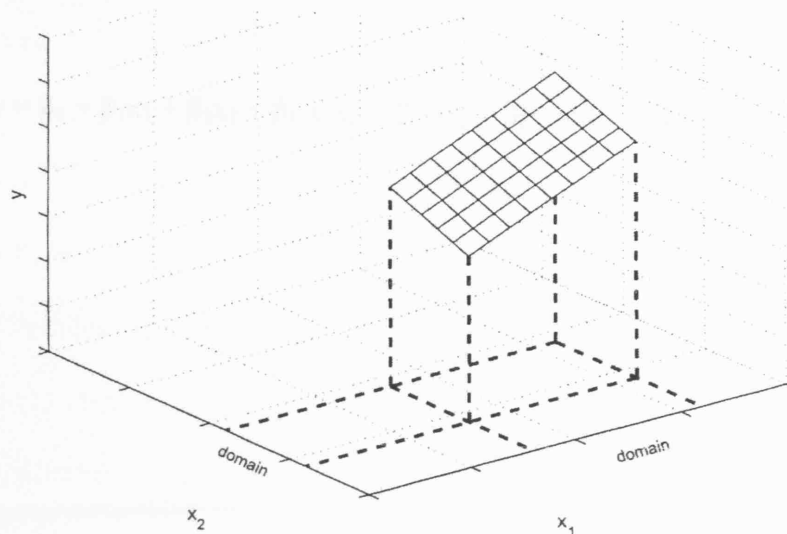
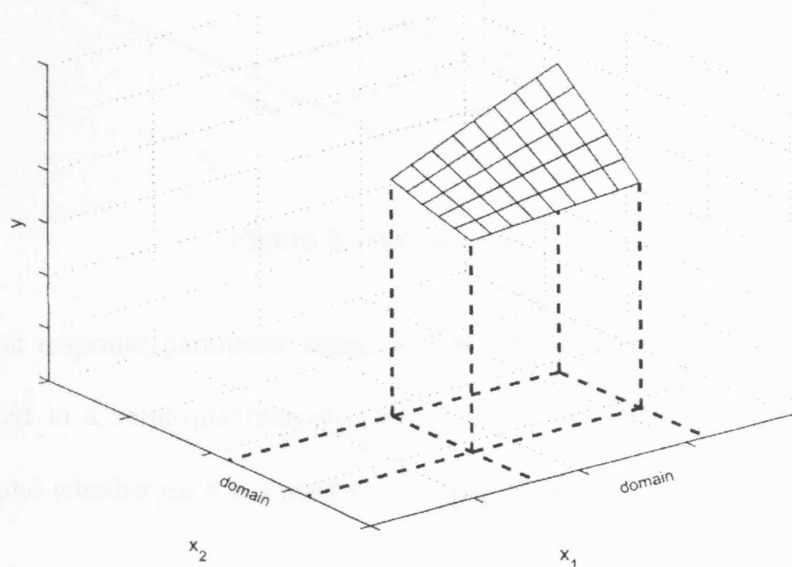


Figure 4. (reproduced from ¹³⁴.)

If a linear model does not provide an adequate fit, a second order polynomial equation may be utilised (Equation 2). The factor-factor interaction term (β_{12}) describes the twist in the plane of the reaction surface (Figure 5).

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + e \quad \text{(Equation 2).}$$

**Figure 5.** (reproduced from ¹³⁴.)

The final and most complex polynomial model is the quadratic model (Equation 3). This represents a curved area of the experimental domain (Figure 6). This model is only used out of necessity in cases where the previous two do not give an adequate fit.

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + e \quad \text{(Equation 3).}$$

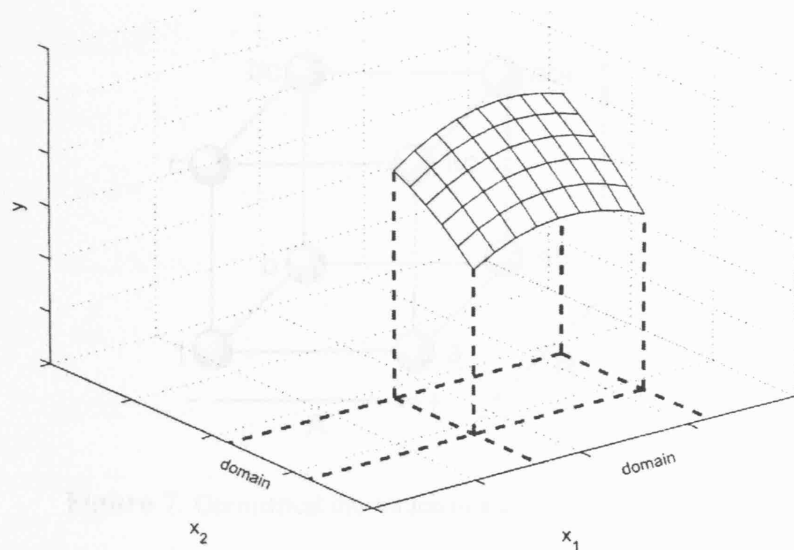


Figure 6. (reproduced from ¹³⁴).

Whilst these response parameter terms do not actually have a physical value, they may be used in a semi-quantitative manner to infer a relative importance of each parameter and whether each is a positive or negative effect.

2.44 Alternative Approaches to One Variable at a Time (OVAT).

The first alternative approach to a one variable at a time approach (OVAT) is a full factorial experimental design; this is conceptually simple and may potentially be carried out without the aid of computer software as later demonstrated in *Section 2.51*. A full fractional factorial experimental design takes each variable at two discrete levels (+1 and -1). Therefore the number of experiments required is 2^n , (where n = number of variables to be examined). This method is ideal in cases where there are low numbers of variables to be examined, but can become unwieldy at higher levels due to the sheer quantity of experiments which must be performed. For example, 7 variables at 2 levels would require 128 experiments, whilst 10 variables at 2 levels would require a massive 1024 experiments to be carried out. From a full factorial experimental design it is possible to calculate both the main effects (*e.g.* A,B or C) as well as all of the factor-factor interactions (*e.g.* AB).

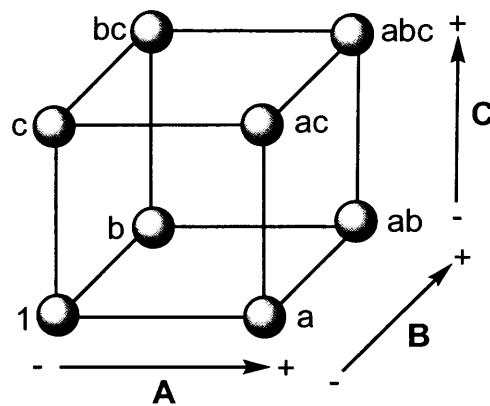


Figure 7. Geometrical illustration of a 2^3 full factorial design.

When higher numbers of variables become involved in the experimental design it is common to resort to a fractional factorial experimental design. This type of design is particularly useful when carrying out initial screening studies since a large number of variables are likely to be needed to be investigated.

In a fractional experimental design, only a subset of experiments from the full design are carried out, giving a good estimate of the main effects. As a consequence, this method is significantly less time consuming, since far fewer experiments are required to gain useful information, but often leads to confounding of factor-factor interactions and thus, the loss of potentially useful information.

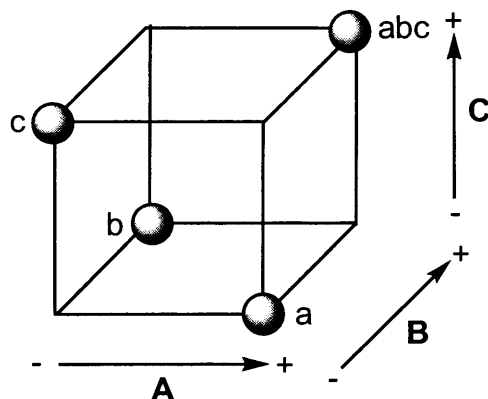


Figure 8. Geometrical illustration of a 2^{3-1} fractional factorial design.

2.45 Determination of Error and Model Significance.

In synthetic chemistry it is fair to assume that a normal or bell-shaped distribution of error is occurring for the response for repetition of a reaction. Replication of a reaction with each variable set at the centre-point may provide an estimate of the random error of the system, but does not adequately give an estimate of the systemic error upon changing from one variable to another. This systemic variation or noise can be determined by the comparison of the calculated model effects (*e.g* A, B or C) against an estimate of systemic experimental error. By the use of least squares fit multiple linear regression it is possible to calculate the residuals (RDS) as the difference between a predicted response at any given value (\hat{y}_i) and measured response (y_i) at a predetermined confidence level (Equation 4).

$$\text{RDS} = y_i - \hat{y}_i \quad \text{(Equation 4).}$$

The use of software to carry out the design of experiments process often gives values for R^2 and Q^2 . R^2 is the goodness of fit, and is calculated according to Equation 5.

$$R^2 = 1 - \frac{\text{SSR}}{\text{SST}} \quad \text{(Equation 5).}$$

An R^2 value of >0.9 is considered excellent, whilst a value of >0.8 is usually considered adequate for the model.

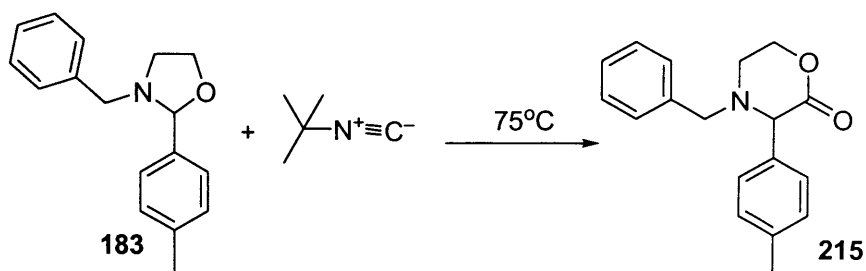
Q^2 represents the goodness of prediction and is calculated according to Equation 6.

$$Q^2 = 1 - \frac{\text{PRESS}}{\text{RDS}} \quad \text{(Equation 6).}$$

Q^2 values of >0.9 are considered excellent, whilst values of >0.5 are usually considered adequate for a screening model.

2.5 Design of Experiments (DoE) for 2-CR Morpholinone Synthesis.

In order to further investigate the formation of morpholinones **214** from an *N*-alkyl oxazolidine and an isocyanide, oxazolidine **183** and *tert*-butyl isocyanide were chosen as the model substrate to be investigated (Scheme 94).



Scheme 94

The factors investigated in this study were solvent type (2 levels), *p*TsOH acid catalyst loading and *tert*-butyl isocyanide loading (Table 6). A full factorial experimental design (resolution V)¹³⁷ with three factors with each at two levels, allowing main factors and interaction between factors to be assessed for importance was carried out as eight experiments plus two control experiments (Table 7). Yields of **215** were determined by HPLC UV peak area integration relative to 1,1,1-trifluorotoluene internal standard at the three reaction times stated in Table 7, and the results after 44 hours were used for further analysis.

	Variable	(-)	0	(+)
A	Acid Catalyst (mol%)	10	30	50
B	Isocyanide (equivalents)	1	1.25	1.5
C	Solvent Type ^a	i	-	ii

^a (i)-DMSO, (ii)-Sulfolane

Table 6. Variables considered, with levels employed in design.

	A	B	C	4h	22h	44h
1	-	-	-	0%	15%	26%
2	-	-	+	0%	3%	4%
3	+	-	-	4%	26%	38%
4	+	-	+	8%	23%	29%
5	-	+	-	0%	16%	27%
6	-	+	+	0%	7%	9%
7	+	+	-	7%	33%	51%
8	+	+	+	12%	24%	36%
9	0	0	-	4%	28%	41%
10	0	0	-	5%	30%	43%

Table 7. Experimental plan and results for DoE #1.

To show the conceptual simplicity of full factorial experimental design, the results have been interpreted both with and without the aid of computer software, although, in the latter case, more information can be gleaned. This is in order to help explain the fundamental principles involved.

2.51 Manual Interpretation of Results by Sign Table.

From the standard model matrix for a 2^3 full factorial design (Table 8), which is graphically depicted in Figure 9, it is possible to calculate the relative effects after 44 hours reaction time for the three variables above - A,B and C according to a second order approximation model.

#	A	B	C	AB	AC	BC	ABC	44 h	
1	-1	-1	-1	+1	+1	+1	-1	26%	1
2	+1	-1	-1	-1	-1	+1	+1	38%	a
3	-1	+1	-1	-1	+1	-1	-1	27%	b
4	+1	+1	-1	+1	-1	-1	+1	51%	ab
5	-1	-1	+1	+1	-1	-1	-1	4%	c
6	+1	-1	+1	-1	+1	-1	-1	29%	ac
7	-1	+1	+1	-1	-1	+1	+1	9%	bc
8	+1	+1	+1	+1	+1	+1	+1	36%	abc

Table 8. Sign Table for 1st DoE.

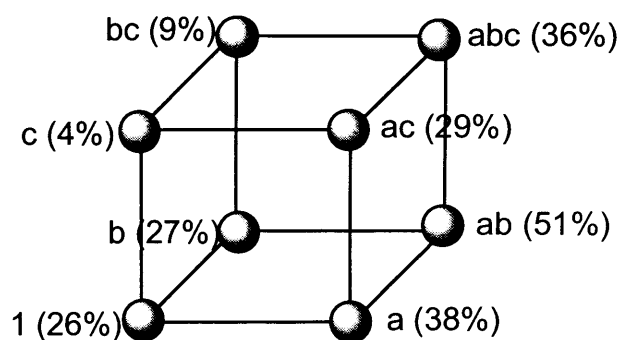


Figure 9.

A (*p*TsOH Acid catalyst (mol%)) = 11

$$A = 1/2[(a-1) + (ab-b) + (ac-c) + (abc-bc)]/4$$

$$\text{so } A = 1/8[(a-1) + (ab-b) + (ac-c) + (abc-bc)]$$

$$\text{so } A = 1/8[(36-26) + (51-27) + (29-4) + (36-9)] = 11$$

B (Isocyanide equivalents) = 3.3

$$B = 1/8[(b-1) + (ab-a) + (bc-c) + (abc-ac)]$$

$$\text{so } B = [(27-26) + (51-38) + (9-4) + (36-29)] = 3.3$$

C (Solvent Type) = -8.0 (in favour of DMSO)

$$C = 1/8[(c-1) + (ac-a) + (bc-b) + (abc-ab)]$$

$$\text{so } C = 1/8[(4-26) + (29-38) + (9-27) + (36-51)] = -8.0$$

AB (Interaction between *p*TsOH equivalents and isocyanide equivalents) = 1.7

$$AB = 1/2[(A_{B+} - A_{B-})]$$

$$A_{B+} = 1/2[(ab-b) + (abc-bc)]/2$$

$$A_{B+} = (\text{effect of A when B is at it's highest level})$$

$$\text{so } A_{B+} = 1/4[(ab-b) + (abc-bc)]$$

$$\text{so } A_{B+} = 1/4[(51-27) + (36-9)] = 13$$

$$A_{B-} = 1/4[(a-1) + (ac-c)]$$

$$\text{so } A_{B-} = 1/4[(38-26) + (29-4)] = 9.3$$

$$\text{so } AB = 1/2[13 - 9.3] = 1.7$$

AC (Interaction between *p*TsOH equivalents and solvent type) = 0

$$AC = 1/2[(A_{C+} - A_{C-})]$$

$$A_{C+} = 1/2[(ac-c) + (abc-bc)]/2$$

$$A_{C+} = (\text{effect of A when C is at it's highest level})$$

$$\text{so } A_{C+} = 1/4[(ac-c) + (abc-bc)]$$

$$\text{so } A_{C+} = 1/4[(29-4) + (36-9)] = 9.0$$

$$A_{C-} = 1/4[(a-1) + (ab-b)]$$

$$\text{so } A_{C-} = 1/4[(38-26) + (51-27)] = 9.0$$

$$\text{so } AC = 1/2[9.0 - 9.0] = 0$$

BC (Interaction between isocyanide equivalents and solvent type) = 0

$$\begin{aligned}
 BC &= 1/2[(B_{C+} - B_{C-})] \\
 B_{C+} &= 1/2[(ab-b) + (abc-bc)]/2 \\
 B_{C+} &= \text{(effect of C when C is at it's highest level)} \\
 \text{so } B_{C+} &= 1/4[(bc-c) + (abc-ac)] \\
 \text{so } B_{C+} &= 1/4[(9-4) + (36-29)] = 3.0 \\
 A_{B-} &= 1/4[(a-1) + (ac-c)] \\
 \text{so } A_{B-} &= 1/4[(51-38) + (26-27)] = 3.0 \\
 \text{so } AB &= 1/2[3.0 - 3.0] = 0
 \end{aligned}$$

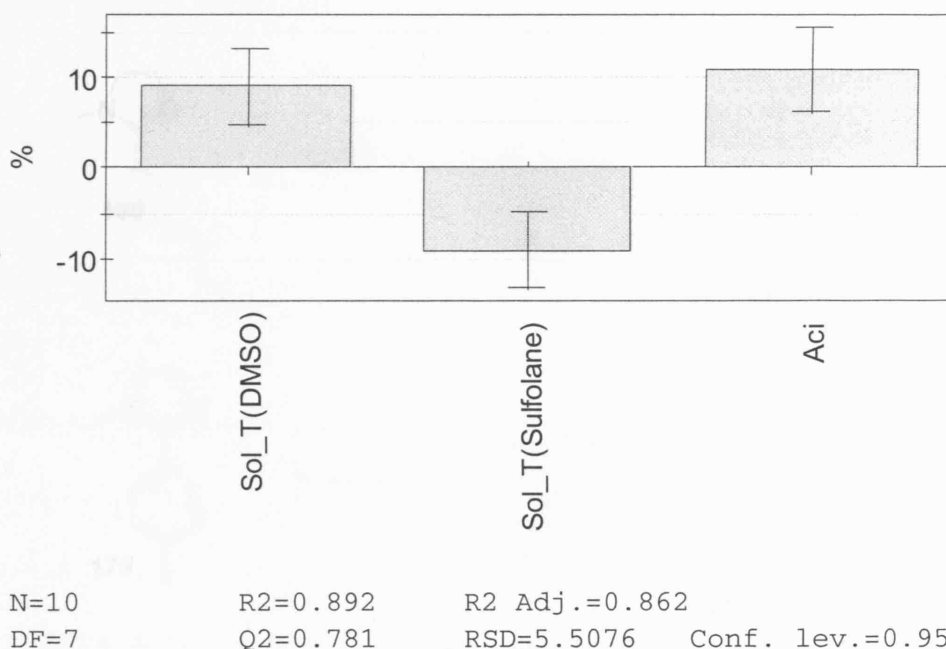
The results give an indication that solvent type is an important factor in favour of DMSO and also that the loading of *p*TsOH is even more important. Adjusting the loading of *tert*-butyl isocyanide appears to have much less of an effect if any. The interaction between *p*TsOH loading and *tert*-butyl isocyanide loading (AB) appears small. There is no interaction effect between solvent type and *p*TsOH equivalents (AC), thereby indicating *p*TsOH is a similar strength acid in both solvents. Similarly, there is no interaction between *tert*-butyl isocyanide equivalents and solvent type (BC), indicating that *tert*-butyl isocyanide behaves similarly in both solvents.

The drawback to using sign tables such as Table 8 for calculation of effects as shown above is that it not possible to draw any conclusions as to the significance of any of these estimated effects since they can not be compared with an estimate of the experimental error variation. In order to do this, interpretation of the data by multiple linear regression is required.

2.52 Interpretation by Least Squares Fit Linear Regression.

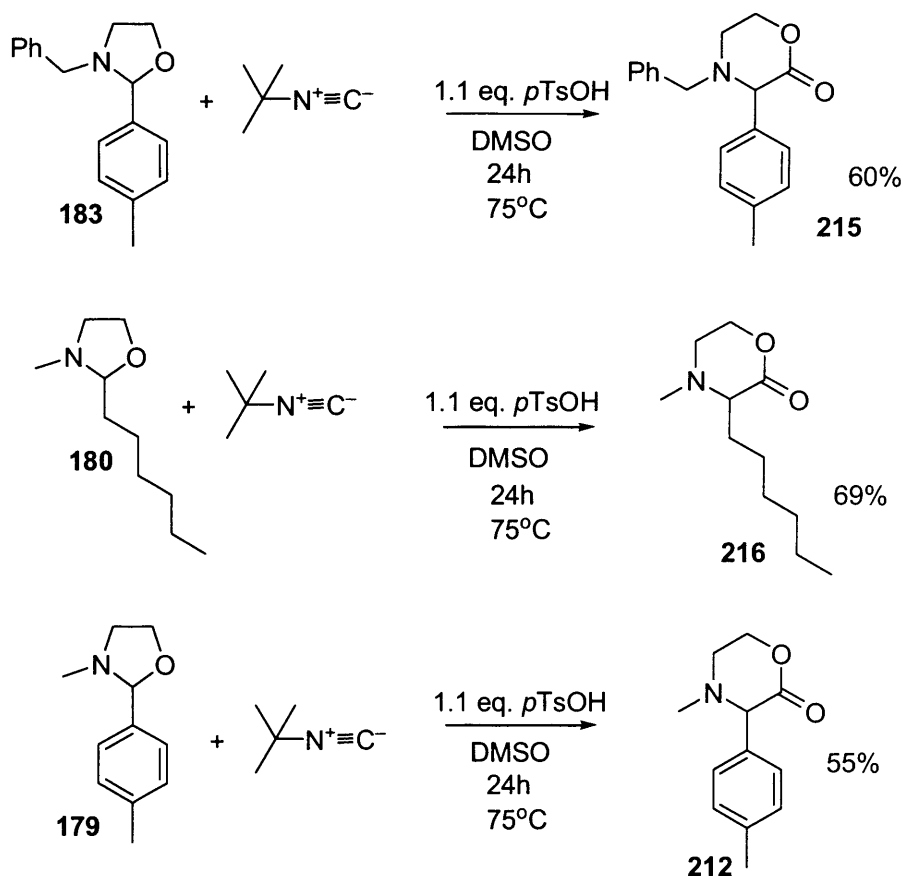
The interpretation of the data using computer software allows for simple calculation of the residuals (RDS), goodness of fit (R^2) and goodness of prediction (Q^2) calculations. The data from Table 7 was analysed by least squares fit linear regression analysis using Modde 7.0^{®138} to give a model where $R^2 = 0.892$, $Q^2 = 0.781$ and RDS = 5.51 at a 95% confidence limit. The data from the model is viewed as a scaled and centred coefficient plot where the sign and size of each coefficient bar

shows the relative effect on the yield and thus the relative importance of the factor in the model (Graph 1). The confidence intervals for this plot are shown on Graph 1 as error bars.



Graph 1. Scaled and centred coefficients for morpholinone synthesis DoE #1.
(ANOVA table and full data in appendix 4.1)

The results above show that solvent type is an important factor, with DMSO superior to sulfolane. *p*TsOH loading is also a factor, with the higher loading level studied resulting in a greater yield. Isocyanide loading had no effect within the levels studied. With this information in hand, the loading of *p*TsOH was increased to 1.1eq. and DMSO was used as the reaction solvent leading to an improved yield of 60% for **215** (Scheme 95). Morpholinone **212** was isolated in 69% yield, using the new conditions, which is a dramatic improvement over the original 3-CR yield of only 36% in Scheme 92, before the DoE optimisation.

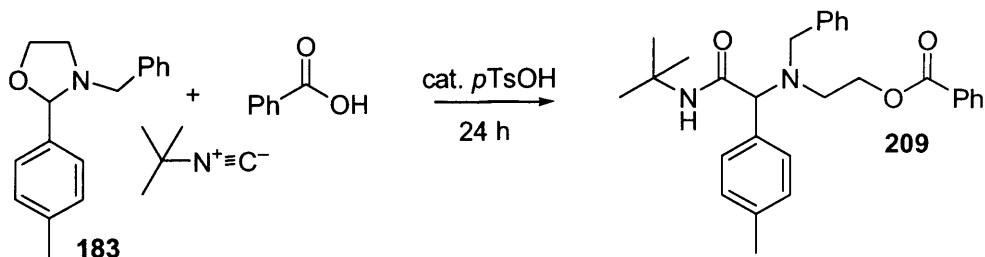


Scheme 95

2.6 Design of Experiments (DoE) Approach to 3-CRs Involving *N*-alkyloxazolidines, Isocyanides and Carboxylic Acids.

Due to the problems associated with the 4-CR (Scheme 90), it was decided to also use a Design of Experiments (DoE) approach for the determination of optimum conditions, particularly those which disfavour the formation of the morpholinone. For experimental simplicity, initially conditions were developed for the 3-CR, with the intention of being able to subsequently carry out the reaction in a four-component fashion without morpholinone side product formation which would be exacerbated by the eliminated water. It was also anticipated that improved conditions would decrease the level of morpholinone side product produced in the 3-CR, enabling the reaction to be carried out under non-anhydrous conditions.

Oxazolidine **183**, *tert*-butyl isocyanide and benzoic acid were used for this investigation (Scheme 96). This substrate was chosen because it had previously given a moderate yield of 44% (*vide supra*, Table 4) and thus had plenty of scope for detectable variation in the yield.



Scheme 96

In order to investigate this reaction, a mixed level fractional factorial experimental design (resolution III)¹³⁹ with 1 factor at 4 levels and 5 factors at 2 levels was planned. This design only allows for main factors to be assessed for importance, and was carried out as 16 experiments plus four control experiments (Table 9). Yields of **209** and **215** were determined by HPLC UV peak area integration against a 1,1,1-trifluorotoluene internal standard, which had been calibrated against previously isolated samples. The variables to be investigated and the levels chosen are shown in Table 9.

	Variable	(-)	0	(+)
A	Temperature (°C)	60	N/A	80
B	Solvent Concentration (M)	0.2	0.3	0.4
C	Benzoic Acid (R5) (equivalents)	1	1.25	1.5
D	Acid Catalyst (mol%)	2	6	10
E	Isocyanide (R4) (equivalents)	1	1.25	1.5
F	Solvent Type (4 types) ^a	-	-	-

^a (i)-Anisole (ii)-EtOAc (iii)-¹PrOH (iv)-MeCN

Table 9. Variables considered, with levels employed in DoE #2.

The data was analysed using MODDE[®] 7.0 software by a least squares fitting model. This resulted in two models, the first for *N*-acyloxyaminoacid amide **209** where R² = 0.922, Q² = 0.844 and RDS = 4.15 at a 95% confidence level and a second model for

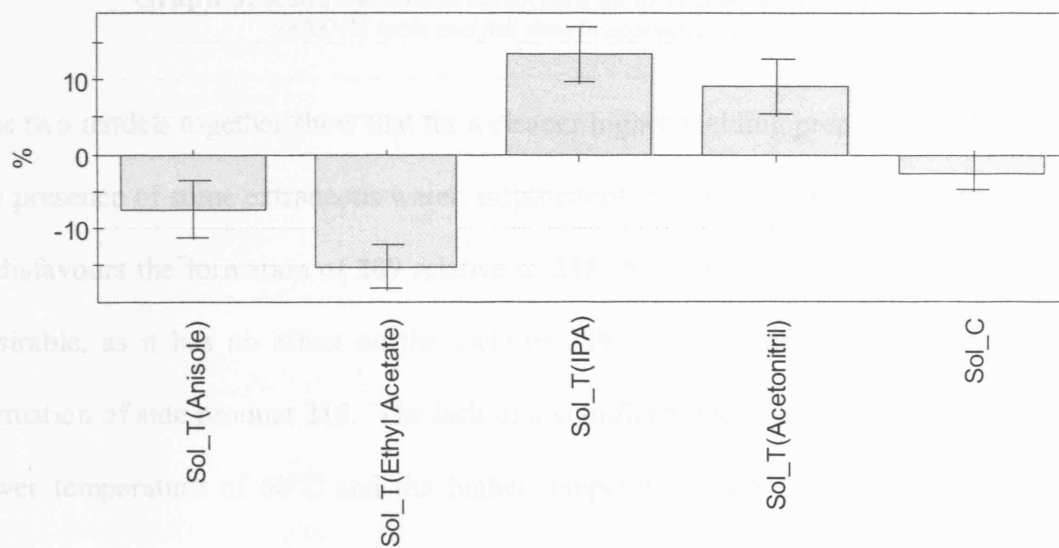
morpholinone **215** where $R^2 = 0.897$, $Q^2 = 0.711$ and RDS = 1.83 at a 95% confidence level.

#	A	B	C	D	E	F	Yield 209	Yield 215
1	-	-	-	+	+	i	48%	26%
2	+	-	-	+	+	ii	44%	23%
3	-	-	-	-	-	iii	65%	18%
4	+	-	-	-	-	iv	67%	30%
5	+	+	-	-	+	i	38%	18%
6	-	+	-	-	+	ii	36%	16%
7	+	+	-	+	-	iii	64%	30%
8	-	+	-	+	-	iv	61%	36%
9	+	-	+	+	-	i	47%	27%
10	-	-	+	+	-	ii	38%	17%
11	+	-	+	-	+	iii	74%	14%
12	-	-	+	-	+	iv	68%	21%
13	-	+	+	-	-	i	54%	24%
14	+	+	+	-	-	ii	33%	13%
15	-	+	+	+	+	iii	68%	25%
16	+	+	+	+	+	iv	57%	29%
17	-	0	0	0	0	ii	41%	18%
18	-	0	0	0	0	ii	42%	18%
19	+	0	0	0	0	ii	40%	19%
20	+	0	0	0	0	ii	38%	18%

(i)-Anisole (ii)-EtOAc (iii)-^tPrOH (iv)-MeCN

Table 10. Experimental plan and results for DoE #2.

For the formation of *N*-acyloxyaminoacid amide **209**, temperature; equivalents of benzoic acid, *p*TsOH and isocyanide and concentration of reactants all had no statistical effect within the parameters investigated. Graph 2 shows that choice of solvent is the most significant factor affecting the yield of *N*-acyloxyaminoacid amide **209**, with isopropanol and, to a lesser degree, acetonitrile, being superior.



N=20
DF=15

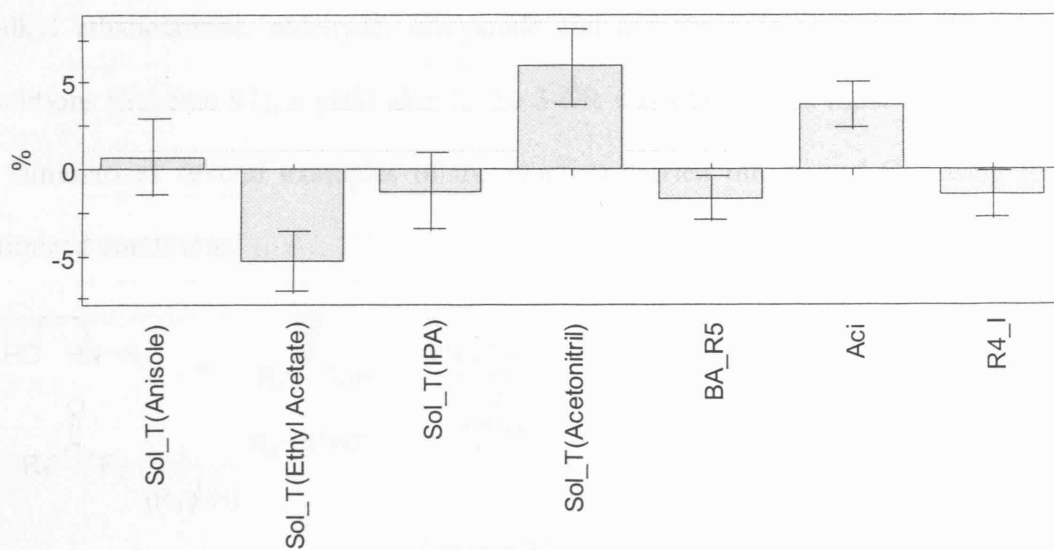
R²=0.922
Q²=0.844

R² Adj.=0.901
RSD=4.1493 Conf. lev.=0.95

MODDE 7 - 26/07/2006 11:01:30

Graph 2. Scaled and centered coefficients for **209** yield.
(ANOVA table and full data in appendix 4.2)

Graph 3 indicates that the factors affecting yield of morpholinone **215** were solvent and *p*TsOH loading. The use of acetonitrile as solvent and a higher loading of *p*TsOH resulted in an undesirable increased yield of morpholinone side product **215**.



N=20
DF=13

R²=0.897
Q²=0.711

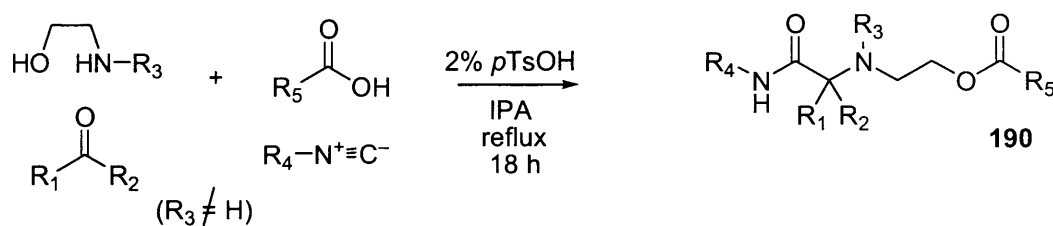
R² Adj.=0.849
RSD=2.3989 Conf. lev.=0.95

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Graph 3. Scaled and centred coefficients for morpholinone **215** yield.
(ANOVA table and full data in appendix 4.2)

The two models together show that for a cleaner higher yielding preparation of **209** in the presence of some extraneous water, isopropanol is a good choice of solvent, since it disfavours the formation of **209** relative to **215**. A lower loading of *p*TsOH is also desirable, as it has no effect on the yield of **209**, while a higher level favours the formation of side product **215**. The lack of a significant yield difference between the lower temperature of 60°C and the higher temperature of 80°C, indicates that the lower temperature should probably be used as there is no benefit indicated by the use of the higher temperature. However it should again be noted that initial work showed that this reaction was prohibitively slow at room temperature or in the absence of an acid catalyst.

The new conditions suggested by this fractional factorial design were expected to reduce the amount of morpholinone **214** produced by hydrolysis of exocyclic imino ether intermediate **213**, without the need to eliminate the presence of water from the reaction conditions. Satisfyingly when the 4-CR reaction was attempted between an *N*-alkyl ethanolamine, aldehyde, isocyanide and a carboxylic acid using the new conditions (Scheme 97), a yield akin to the 3-CR was obtained in most cases. Table 11 summarises several examples of the reaction carried out as a 4-CR using the optimized conditions.



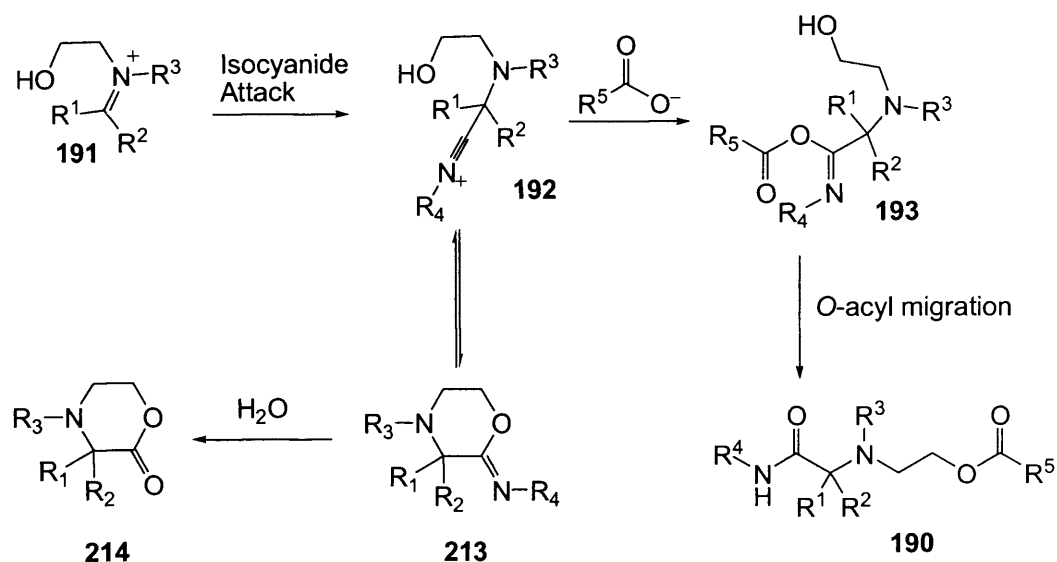
Scheme 97

R ₁	R ₂	R ₃	R ₄	R ₅	Yield	Product
<i>p</i> Me-C ₆ H ₄	H	Me	^t Bu	Ph	68%	197
<i>n</i> C ₆ H ₁₃	H	Me	^t Bu	Ph	66%	201
<i>n</i> C ₆ H ₁₃	H	Me	Cy	Ph	43%	203
<i>p</i> MeO-C ₆ H ₄	H	Me	^t Bu	Ph	66%	207
<i>p</i> O ₂ N-C ₆ H ₄	H	Me	^t Bu	Ph	30%	208

Table 11. 4-CR under new conditions.

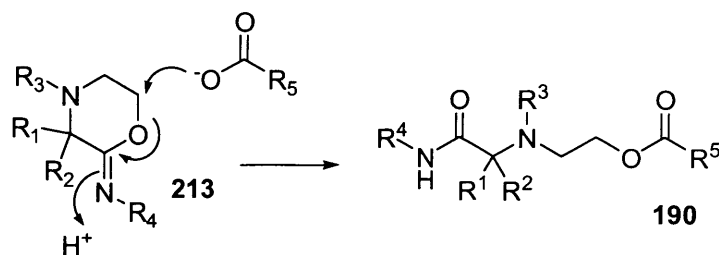
2.71 Isolation of Exocyclic Imino Ether Intermediate **213**.

The suggested mechanism (Scheme 98) for the formation of both *N*-acyloxyethylamino acid amides **190** and morpholinones **214** involves the existence of exocyclic imino ether intermediate **213**.



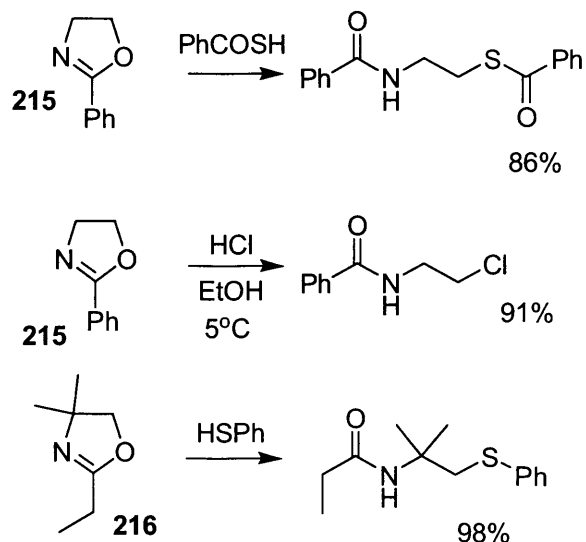
Scheme 98

It was suggested at this juncture that direct formation of *N*-acyloxyethylamino acid amides **190** might in fact be facilitated directly by a ring opening reaction on the electrophilic cyclic imino ether intermediate **213** with no subsequent rearrangement necessary (Scheme 99).



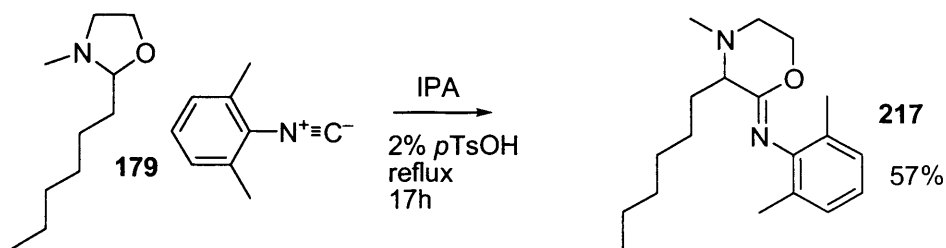
Scheme 99

This mechanism is conceptually similar to the work of Fry,¹⁴⁰ Goldberg and Kelly¹⁴¹ and Wehrmeister¹⁴² (Scheme 100) in which oxazolines **215** & **216** are cleaved by the direct action of a nucleophilic species to form an amide leaving group, except that in the above case of an oxazolidine the N=C double bond is exocyclic.



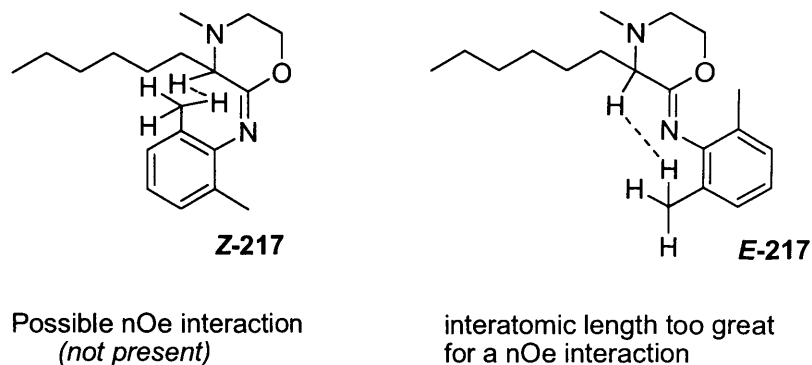
Scheme 100

Isolation of an imino ether intermediate was achieved initially in a reaction of oxazolidine **179**, with 2,6-dimethylphenyl isocyanide, to form the stable product **217** (Scheme 101).



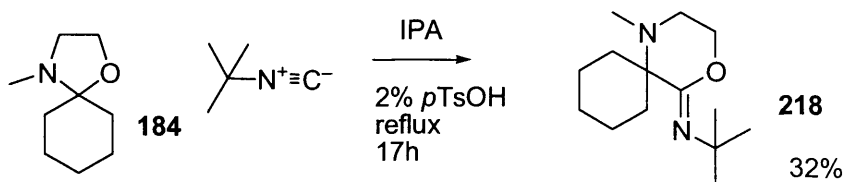
Scheme 101

The *E* regioselectivity of **217** was proven by nOe studies (Scheme 102). No nOe enhancement was observed between the aryl-CH₃ & the tertiary-CH as shown in Scheme 102.



Scheme 102

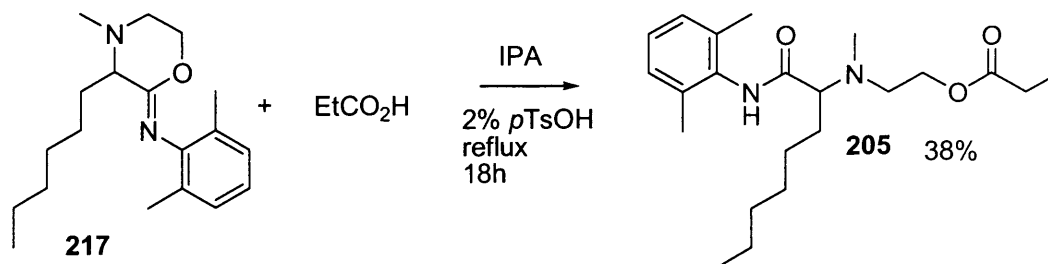
Imino ether **217** was stable at room temperature in the atmosphere for at least 6 months. This stability was thought to be afforded by conjugation with the aromatic group adjacent to the C=N, but even more so by the large steric bulk of the 2,6-disubstituted aryl group. It was not possible to isolate corresponding imino ethers derived from simple alkyl or phenyl isocyanides and aldehyde derived oxazolidines. However, the use of *tert*-butyl isocyanide with ketone derived oxazolidine **184**, with its quaternary centre, affords stable imino ether **218**, in 32% yield (Scheme 103). Once again, this is probably due to the increased steric bulk of the cyclohexyl group making hydrolysis more difficult.



Scheme 103

When imino ether **217** was heated with 2 mol% of *p*TsOH and an equimolar amount of propionic acid, the corresponding *N*-acyloxyethylamino acid amide **205** was isolated in 38% yield (Scheme 104). This experiment was absolutely crucial since it proves beyond doubt that either the direct attack of the carboxylate on the imino ether

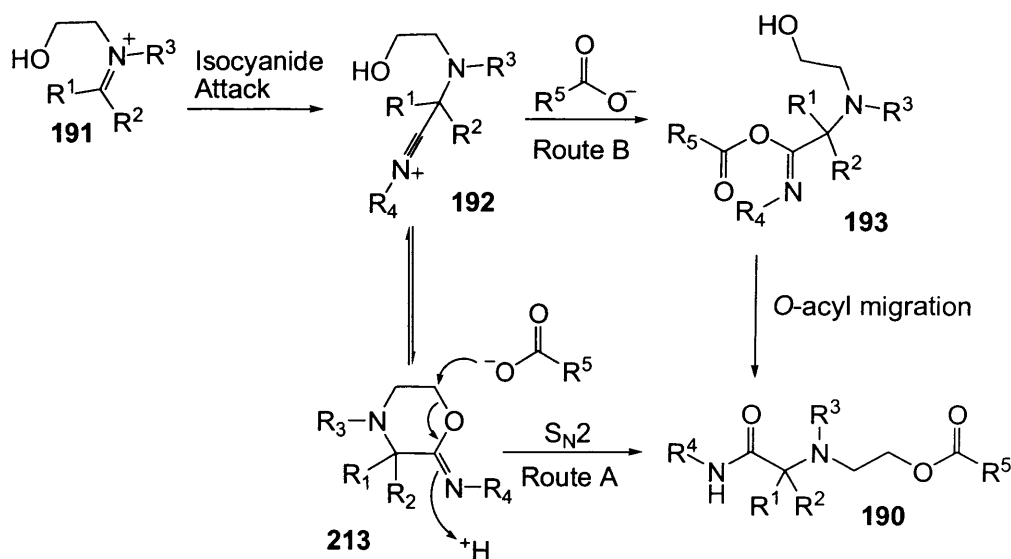
intermediate **217** is possible, or otherwise, that the ring closure of the hydroxyl group on to the nitrilium cation is reversible. This seems counterintuitive but if this ring closure was not irreversible then the Ugi reaction could not be carried out in alcoholic solvents, which they of course almost invariably are, without isolation of imino ether structures.



Scheme 104

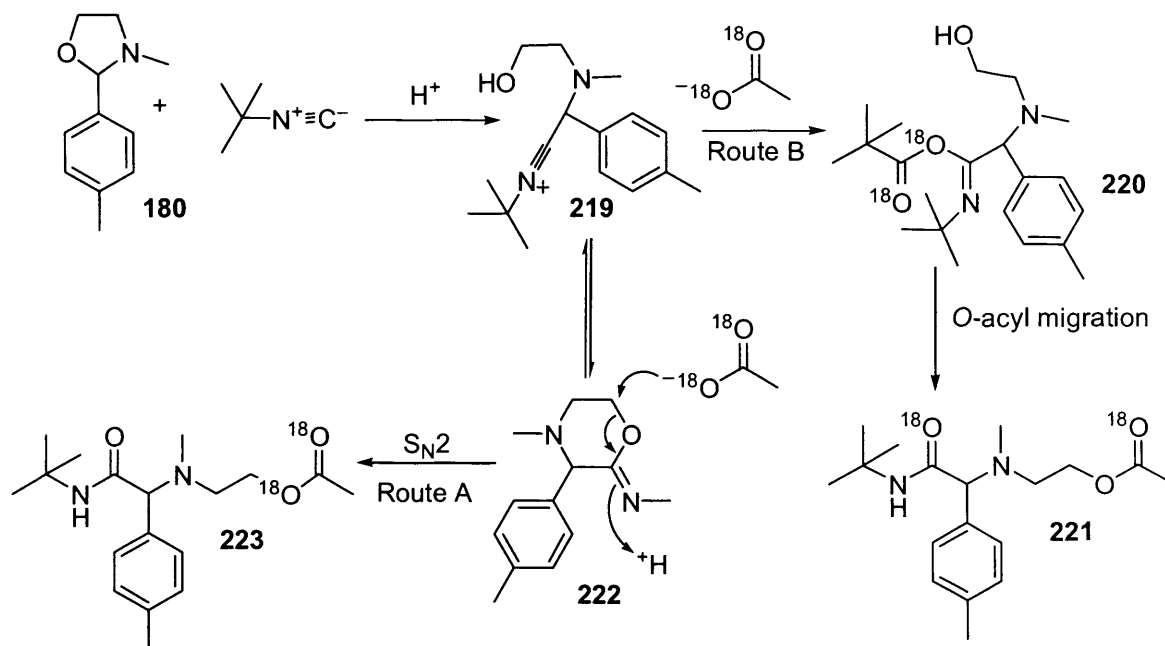
2.72 Mechanistic Studies Including use of $^{18}\text{O}_2$ Labelled Acetic Acid.

Scheme 105 shows two plausible mechanisms for the reaction between an *N*-alkyloxazolidine an isocyanide and a carboxylic acid, either or both of which were considered to be in operation at this stage of the research. As indicated, one of these (Route A), involves direct attack on the exocyclic imino ether intermediate **213** by the carboxylate anion, whilst the second (Route B), requires capture of the nitrilium cation **192** by carboxylate and subsequent *O*-acyl migration.



Scheme 105

In order to clarify the mechanism, $^{18}\text{O}_2$ labelled acetic acid was selected as the acid component of a three-component reaction with oxazolidine **180**, and *tert*-butyl isocyanide. The position of the labelled oxygen atoms in the product of this reaction will be different depending on the mechanistic pathway followed (Scheme 106).



Scheme 106

Thus, **221** will be formed by route B involving capture of the nitrilium cation by the carboxylate anion followed by *O*-acyl migration, whilst **223** is produced by route A which requires acid catalysed ring opening of the exocyclic imino ether **222** by S_N2 attack on the sp^3 carbon by the carboxylic acid. This reaction was carried out in duplicate using both doubly ^{18}O labelled acetic acid and also a standard or blank reaction in which non-labelled acetic acid was used.

Tandem MS/MS fragmentation studies (Figures 10 & 11) on the product of this reaction, by comparison with the product using non-labelled acetic acid **224** strongly suggests **221** to be the exclusive structure. This result indicates that carboxylic acids definitely react by the originally suggested route B, *via* trapping the nitrilium cation with ensuing *O*-acyl migration. The formation of the exocyclic imino ether **222** must therefore be considered as an undesirable parasite reaction.

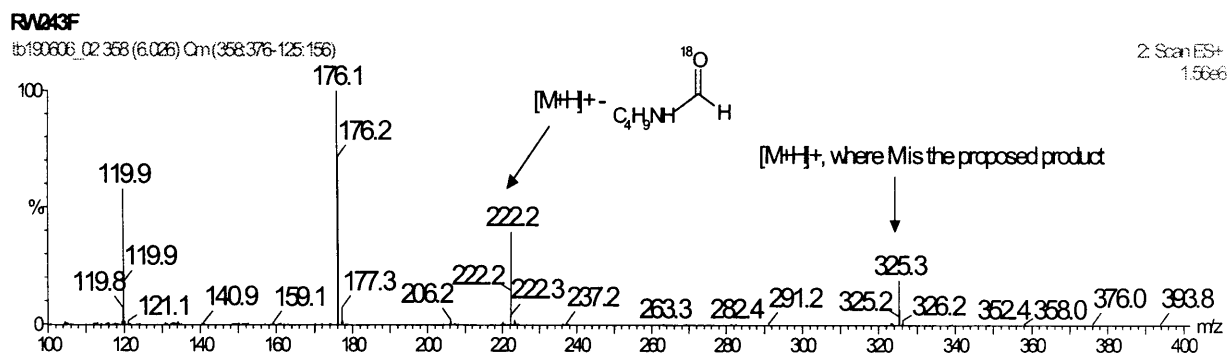


Figure 10. MS-MS fragmentation of $^{18}O_2$ labelled product **221**.

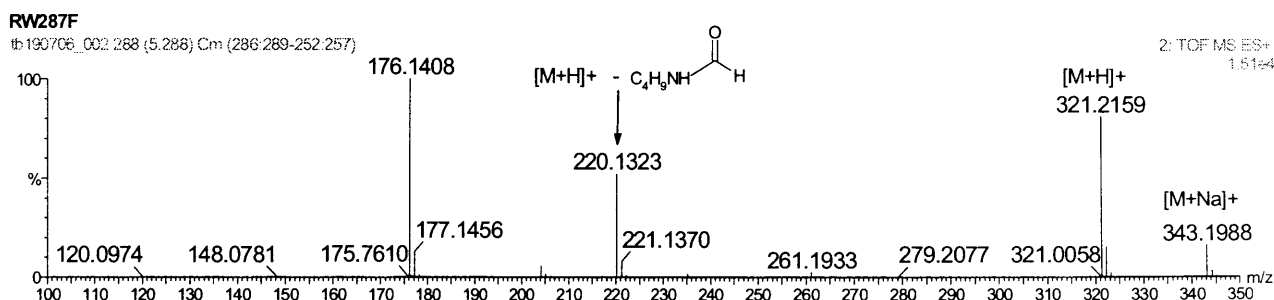
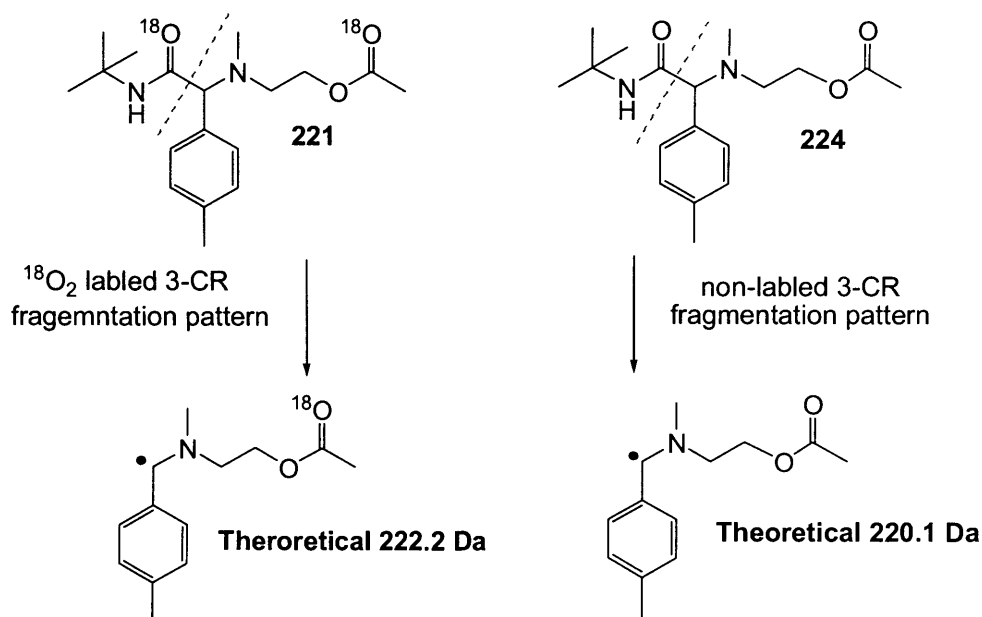


Figure 11. MS-MS fragmentation of non-labelled product **224**.

Fragmentation of the $[M+H]^+$ ion, ($m/z = 321$), of **221**, was achieved by in-source collision induced dissociation (CID). The in-source CID mass spectrum (Figure 10)

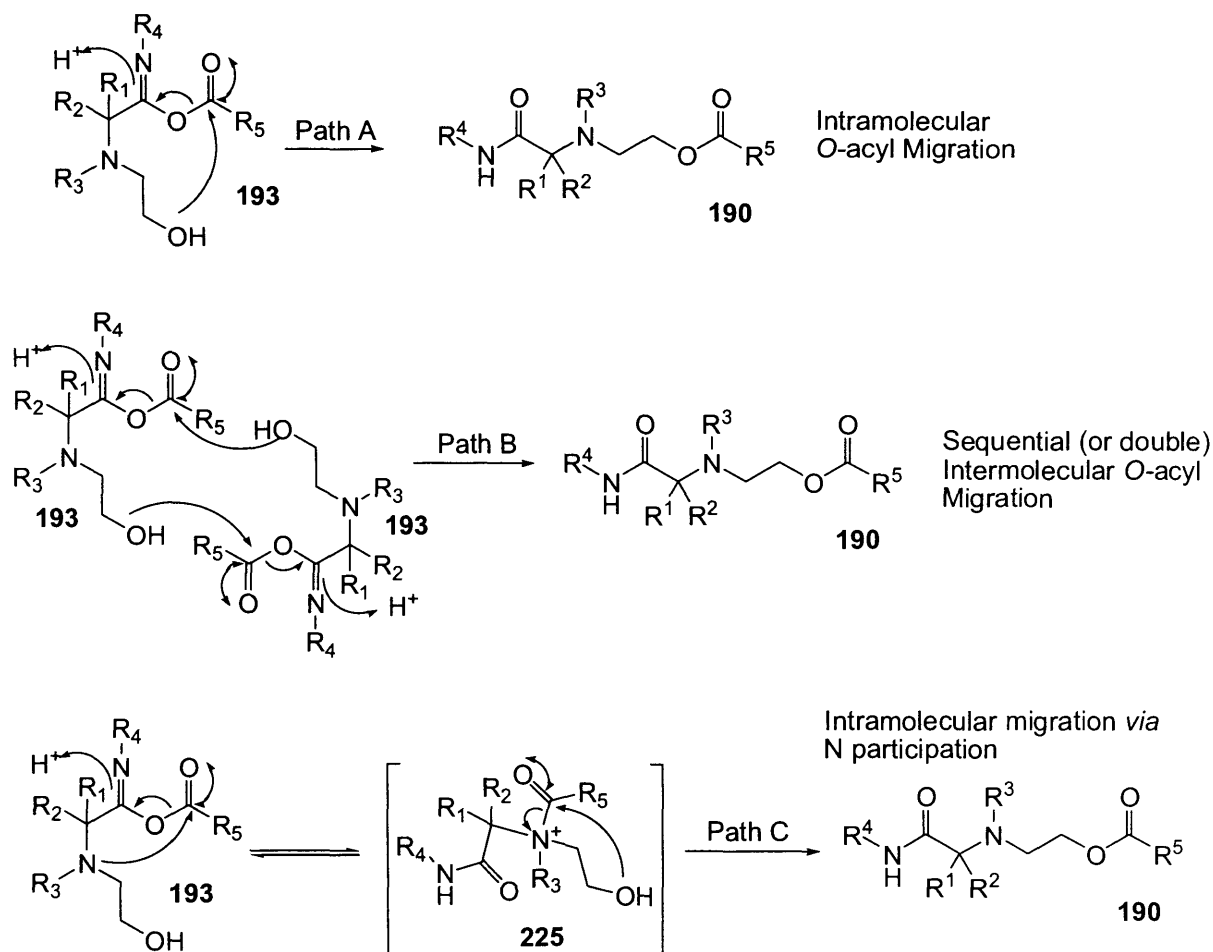
for the labelled compound **221** showed the fragment ion at $m/z = 222.2$, consistent with $[M+H - C_4H_9NHC^{18}OH]^+$: a loss of 103 Da. The in-source CID mass spectrum for the non-labelled compound **224** (Figure 11) showed the fragment ion at $m/z = 220.1$, consistent with $[M+H - C_4H_9NHCOH]^+$: a loss of 101 Da. These fragmentation patterns are indicated in Scheme 107.



Scheme 107

Since the mechanistic pathway had now been firmly established to require attack of a carboxylate anion upon the nitrilium cation **192** and subsequent *O*-acyl migration, some thought was given to this *O*-acyl migration step. This may possibly occur in either intra or intermolecular fashion. Thus, as shown in Scheme 108, hydroxyl group participation can occur either in the intramolecular mode involving an eight-membered ring tetrahedral intermediate (Path A), or in the intermolecular mode, which would probably involve sequential transfer (Path B). An alternative intramolecular scenario (Path C) involving the tertiary amino group of the original oxazolidine is also shown. In this instance, the more nucleophilic tertiary amino group is used instead of the hydroxyl group *via* a 5-membered ring intermediate to

generate an acylammonium cation **225** which can then undergo a second intramolecular transfer step using the pendant hydroxyl group.



Scheme 108

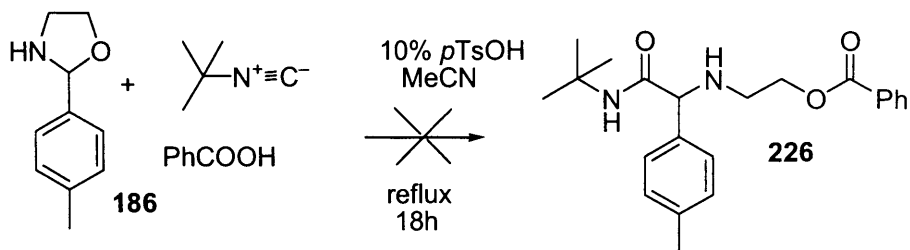
A great deal of effort was put into the design of potential crossover experiments to differentiate between these three possible *O*-acyl migration pathways shown in Scheme 108, but sadly, no simple experiments could be devised.

2.73 Use of *NH* Oxazolidines and Mechanistic Implications.

Ugi reactions using ethanolamine as the amine component have been reported to occur in high yield in MeOH at room temperature in the absence of an acid catalyst, with no requirement for protection of the hydroxyl group (*vide supra*, Schemes 66 & 67).^{99,100} In accord with this observation, Zhang and co-workers have shown that

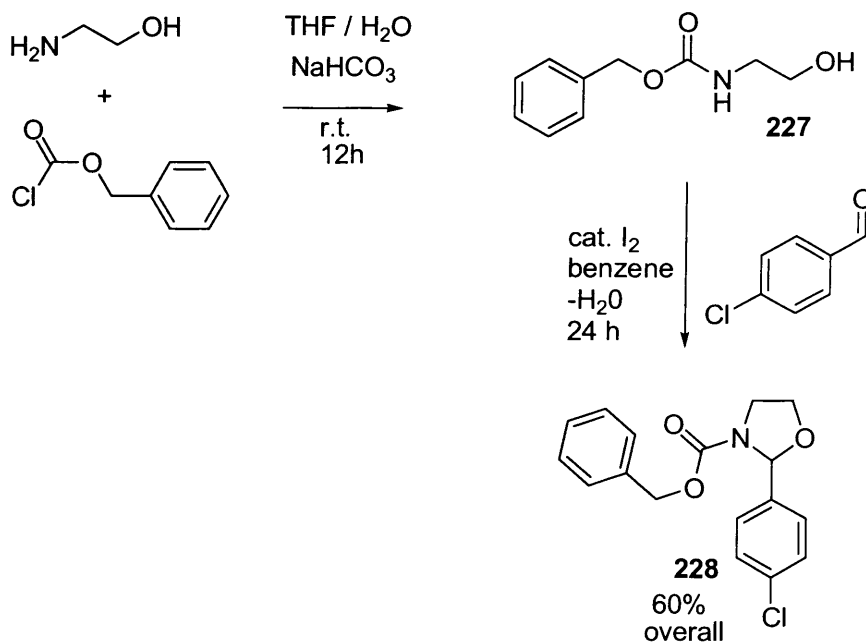
bifunctional aldehyde-carboxylic acids undergo a successful U-4C-3CR using ethanolamine as the amine component, again, with no protection of the pendant alcohol moiety necessary (*vide supra*, Scheme 49).⁸²

However, initial attempts during the early stages of this research prior to the DoE optimisation to use oxazolidine **186** which possesses a secondary *NH* amino group in a 3-CR with benzoic acid and *tert*-butyl isocyanide using MeCN as solvent resulted in a complex mixture of products, with no Ugi product **226** detectable by crude ¹H NMR analysis (Scheme 109).



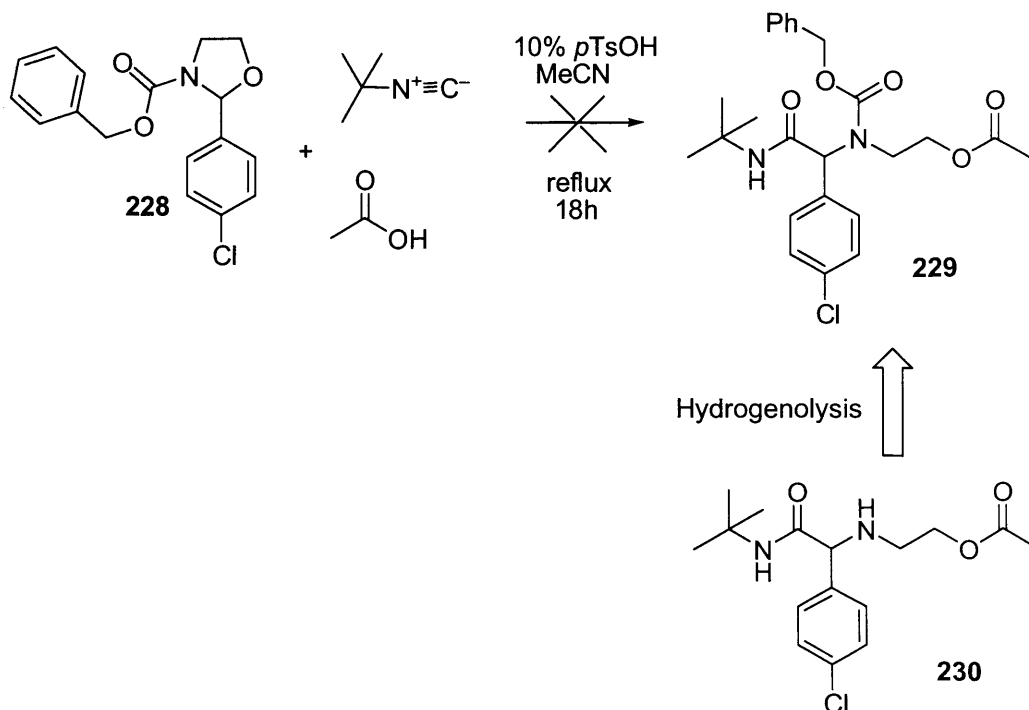
Scheme 109

Since this reaction had been unsuccessful, Cbz-protected oxazolidine **228** was prepared from ethanolamine over two steps (Scheme 110) in order to investigate its use in an IMCR, whereby subsequent deprotection could be carried out to give a similar secondary amine product **230** to the intended product above **226** (Scheme 111).



Scheme 110

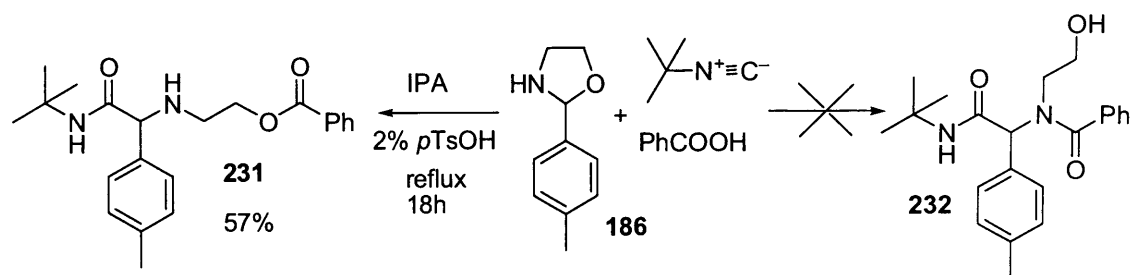
When this Cbz-protected oxazolidine **228** was reacted with acetic acid and *tert*-butyl isocyanide, no reaction occurred; this was thought to be due to the decreased reactivity of the carbamate moiety, hindering ring opening to an electrophilic iminium ion (Scheme 111).



Scheme 111

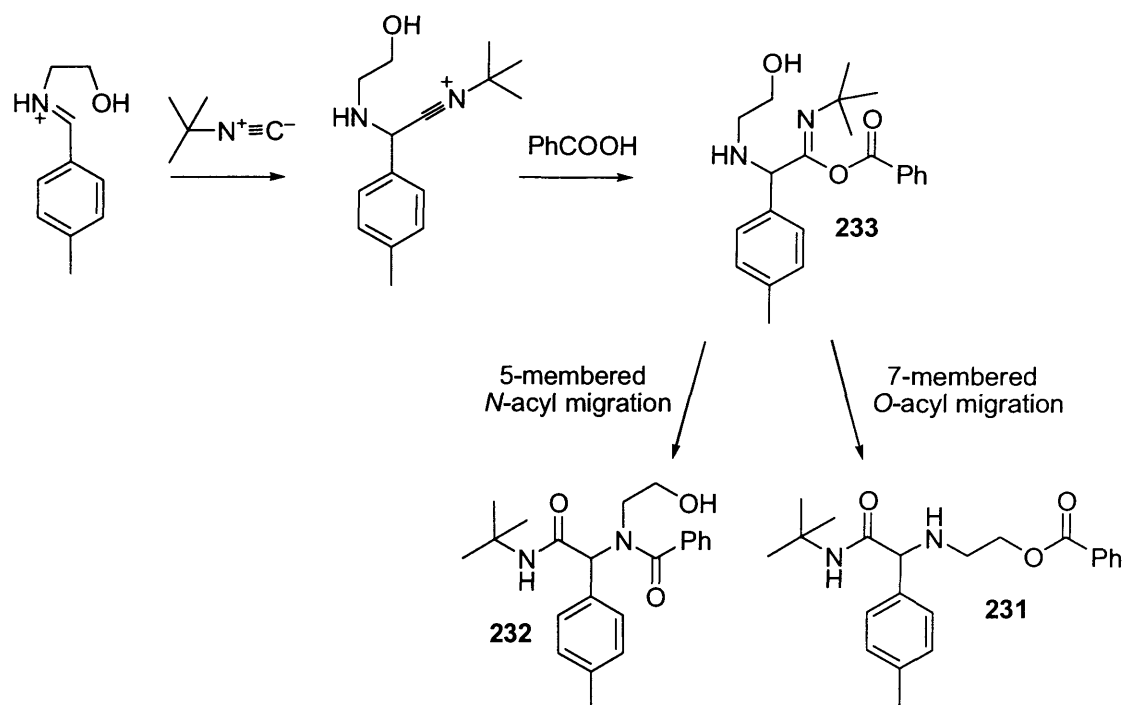
Since, the above work was carried out prior to the DoE optimisation of the 3-CR conditions (*vide supra*, Section 2.6), it was therefore decided to reinvestigate the

reaction of ethanolamine derived *NH*-oxazolidines under the new conditions. An Ugi type reaction of the type previously reported in which the hydroxyl group merely acts as a spectator was anticipated. It was therefore extremely surprising when moderate yields of the *O*-acyl migration product **231** were isolated and no detectable *N*-acyl migration product (Ugi type) **232** was formed (Scheme 112).



Scheme 112

This was an unexpected result, since it was thought that the relative rate of acyl transfer to the secondary amino group in intermediate **233** would be much faster than to the hydroxyl group due to both the greater nucleophilicity of the amine nitrogen atom and the entropically favoured 5-exo-trigonal transition state for *N*-acyl migration as opposed to the 7-exo-trigonal transition state for the *O*-acyl transfer (Scheme 113).



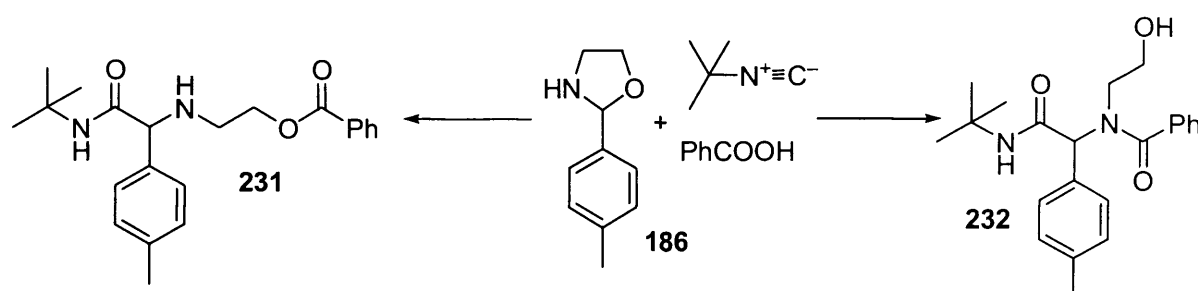
Scheme 113

In order to investigate this singularity, oxazolidine **186**, *tert*-butyl isocyanide and benzoic acid were reacted under a variety of selected reaction conditions (Scheme 114). Table 12 shows that interestingly, an acid catalyst is not required for either the Ugi reaction or the formation of the *N*-acyloxyamino acid amide **231** from secondary amine derived *NH*-oxazolidines and it is moreover in fact, detrimental to the yield.

When MeOH was used at room temperature, 45°C or at reflux (65°C), no *N*-acyloxyamino acid amide **231** was isolated, but instead, the Ugi product **232** was formed. Very curiously, the selection of IPA at reflux gave only *N*-acyloxyamino acid amide **231**, whilst at room temperature; only the Ugi product **232** was isolated. This was the case at both 1 Molar reaction concentration and at the standard Ugi reaction literature concentration of 0.4 Molar (with respect to each of the three components). Ethanol at reflux gave a mixture of both products, whilst a room temperature reaction gave only Ugi product **232**. A room temperature reaction using *tert*-butanol gave only Ugi product **232**, whilst *tert*-butanol at reflux favoured *N*-acyloxyamino acid amide **231**, with some Ugi product **232** also being formed (12%).

This observation however, could be attributed to the almost complete loss of solvent from the reaction mixture as a result of crystallisation in the condenser.

The results of these experiments are a little confusing, but it seems that higher temperatures favour *O*-acyl migration, and that solvent choice is also an important contributing factor. The results are further confused by the fact that mixed reaction mixtures are obtained for both MeOH and IPA at 110°C in a monomode microwave reactor.



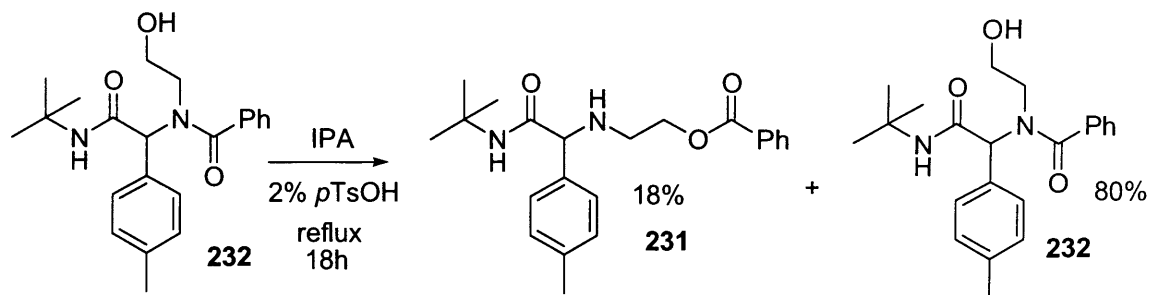
Scheme 114

Temp (°C)	Solvent	Conc. (M)	Time (h)	<i>p</i> TsOH (mmol)	Yield 231	Yield 232
82	IPA	1	18	2	57%	0%
82	MeCN	1	18	2	None present by crude ¹ H NMR	
25	MeOH	0.4	42	0	0%	90%
25	MeOH	0.4	42	2	0%	81%
82	IPA	1	18	0	70%	0%
45	MeOH	0.4	18	0	0%	84%
65	MeOH	0.4	18	0	0%	80%
25	IPA	1	42	0	0%	66%
25	IPA	0.4	42	0	0%	60%
78	EtOH	1	18	0	30%	32%
25	EtOH	1	42	0	0%	71%
83	^t BuOH	1	18	0	48%	12%
25	^t BuOH	1	42	0	0%	48%
110*	MeOH	0.4	0.17	0	17%	51%
110*	IPA	0.4	0.17	0	24%	44%

*- monomode microwave reactor.

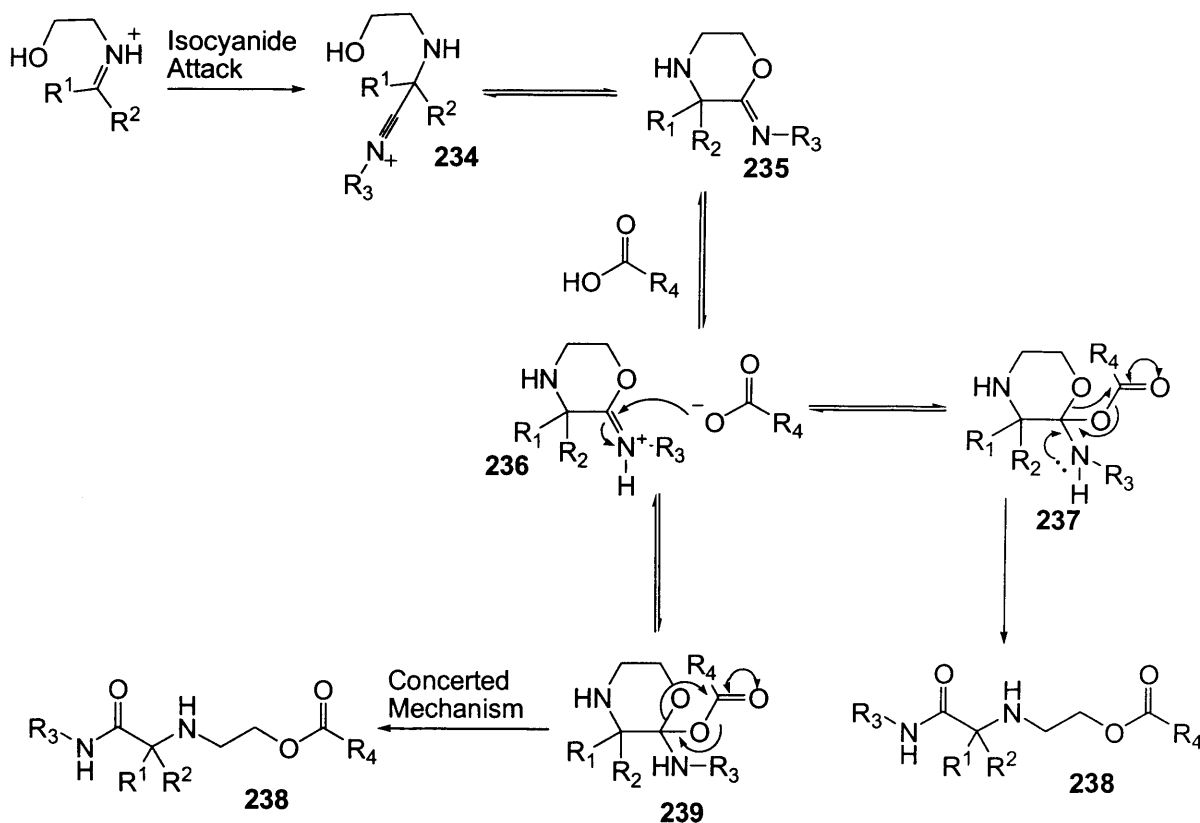
Table 12. Variation of conditions for Scheme 114.

Moreover, when the Ugi product **232** was refluxed in IPA overnight in the presence of 2 mol% *p*TsOH, 18% conversion to the *O*-acyl migration product **231** was observed (Scheme 115). This result is somewhat counterintuitive since, on thermodynamic grounds an amide is thought to be much less reactive than an ester.



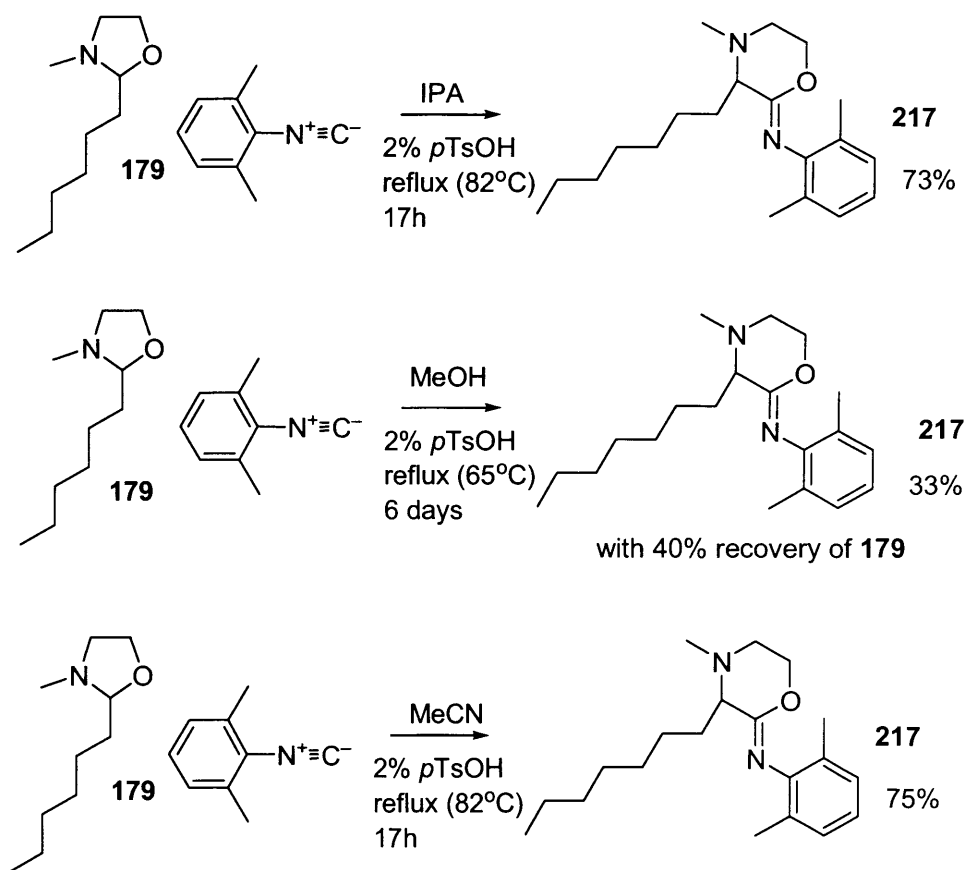
Scheme 115

Upon protonation of the imino ether nitrogen of intermediate **235** it is possible that the carboxylate anion may reversibly attack this electrophilic species to form **239** which can then undergo migration either *via* a concerted mechanism or *via* assistance from the nitrogen lone pair (Scheme 116). This intermediate **239** is unstable and must lose either the carboxylate which will lead back to the exocyclic imino ether **235**, or it is theoretically possible that a migration may occur *via* a concerted mechanism (Scheme 116). This may explain why the exclusive formation of the *O*-acyl migration product **238** occurs under certain conditions with the absence of the *N*-acyl migration product (Ugi type) **240**.



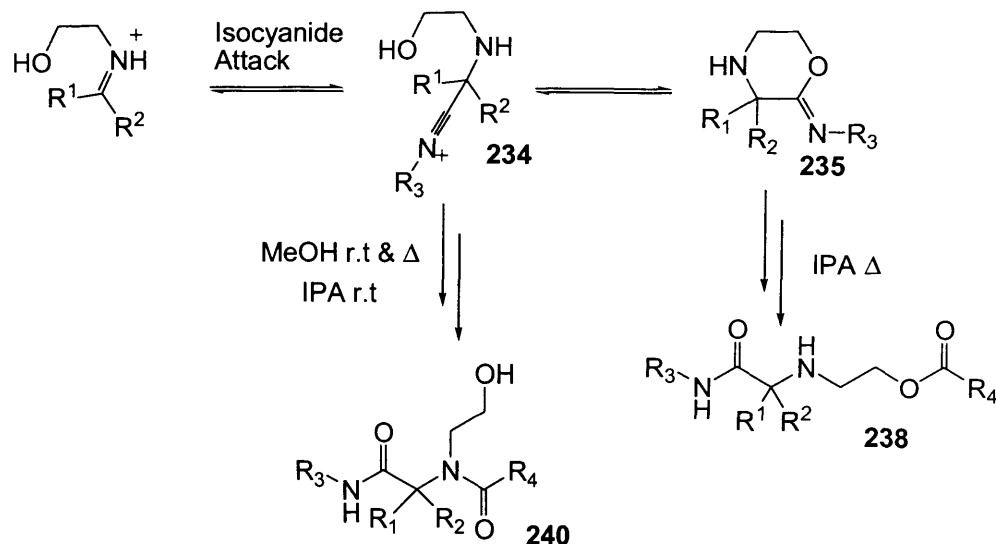
Scheme 116

It was not possible to isolate a stable exocyclic imino ether **235** from a secondary amine derived *NH*-oxazolidine. Therefore for the purpose of gauging relative rates of formation of the exocyclic imino ether **235**, oxazolidine **179** was used (Scheme 117). The formation of *N*-alkyl imino ether **217** in the absence of a carboxylic acid or other nucleophile proceeds significantly faster in IPA at reflux than when the reaction is carried out in MeOH at reflux (Scheme 117). A significantly lower yield (33%) of the imino ether **217** was formed even after a prolonged time of 6 days when the reaction was carried out in MeOH. This reaction time is far greater than the timeframe normally required for *N*-acyloxyamino acid amide **190** formation in the previously discussed three-component reactions. It is thereby assumed that the formation of the secondary amine exocyclic imino ether intermediate **235** in the above reaction mechanism (Scheme 116) would similarly be significantly slower in MeOH than in IPA.



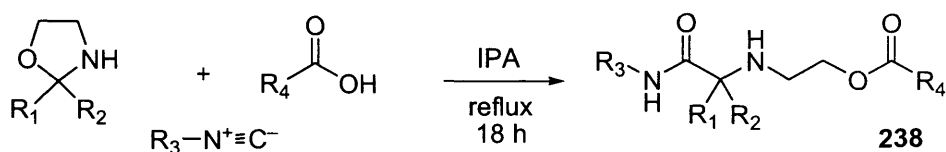
Scheme 117

With this assumption in hand it is proposed that the comparative rate of formation of the two different products **232** and **231** (Scheme 113) is dependant upon the relative population of the *NH* exocyclic imino ether intermediate **235** (Scheme 118). Intermediate **235** is proposed above in Scheme 116 to be an integral steppingstone for the formation of the *N*-acyloxyamino acid amide product **238**, thus, if only small amounts are present at steady state then the rate of formation of the *N*-acyloxyamino acid amide **238** will be low. Conversely, the formation of the Ugi product **240** will occur easily *via* the nitrilium ion **234** (Scheme 118). This argument also helps explain the difference in product ratios upon change of reaction temperature, whereby formation of an *NH* exocyclic imino ether **235** is theorised to be faster at higher temperatures.



Scheme 118

Three examples of this reaction were carried out in order to show a degree of generality (Scheme 119, Table 13).



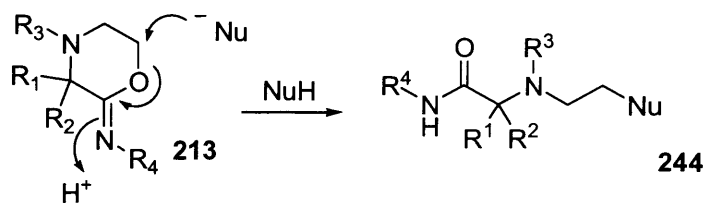
Scheme 119

Oxazolidine	R ₁	R ₂	R ₃	R ₄	Yield	Product
186	<i>p</i> Me-C ₆ H ₄	H	^t Bu	Ph	90%	231
187	Me	Me	^t Bu	2-(3-indole)ethyl	38%	241
187	Me	Me	^c C ₆ H ₁₁	Ph	37%	242
187	Me	Me	^t Bu	Ph	37%	243

Table 13. Examples of 3-CR between an *NH*-oxazolidine, an isocyanide and a carboxylic acid.

2.74 Acidic Nucleophiles for 3-CR with Oxazolidines and Isocyanides.

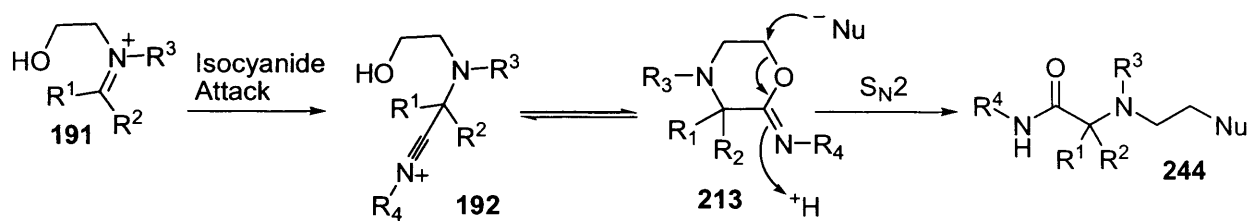
Despite the fact that the ¹⁸O₂ acetic acid labelling experiments had clearly demonstrated in the previous section that carboxylic acids were unable to directly attack the exocyclic imino ether intermediate **213**, it was apparent that other nucleophiles would still be able to achieve this S_N2 type of attack (Scheme 120).



Scheme 120

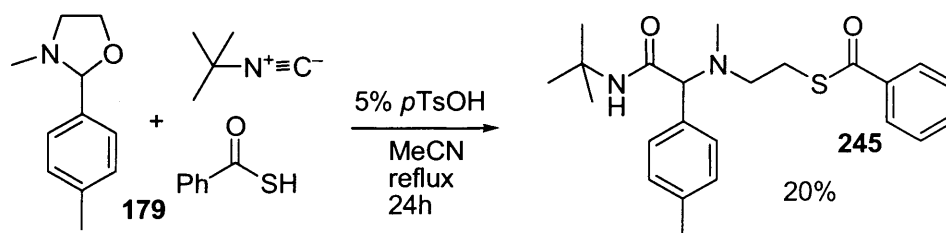
This reaction is definitely expected to be able to occur since it is so conceptually similar to the previously discussed reactions of Fry,¹⁴⁰ Goldberg & Kelly¹⁴¹ and Wehrmeister¹⁴² (*vide supra*, Scheme 100) between an oxazoline and thiobenzoic acid, thiophenol or HCl in a protic acid assisted $\text{S}_{\text{N}}2$ reaction. This type of reaction has one clear benefit over the majority of IMCRs which use the ubiquitous carboxylic acid as a nucleophile, in that a stable product is directly formed by the use of any nucleophile in an irreversible step without the requirement for a final acyl migration step of the α -adduct. This type of α -addition to form a stable α -adduct is seen in the Ugi reaction when water,^{44,58,90} hydrogen selenide⁹¹ or hydrogen thiosulfate⁹¹ are used (*vide supra*, Scheme 58).

In order for a nucleophile to be effective in this type of reaction it must fulfil two fundamental requirements. Firstly, it must be acidic in order to protonate the nitrogen atom of the imino ether functionality to activate it towards nucleophilic attack, although in this case, 5% *p*TsOH is also being used as an acidic catalyst to facilitate this. A strongly acidic nucleophile should be deprotonated in the predominately basic reaction mixture and thus rendered significantly more nucleophilic as its corresponding anion. Secondly, the nature of the nucleophile must be such that it will attack the carbon atom of the exocyclic imino ether intermediate **213** α to the oxygen atom as seen above and not the nitrilium ion **192** present before the formation of the exocyclic iminoether intermediate **213**. Attack on the nitrilium ion **192** by alternative nucleophiles will not give the desired product and in most cases will not give a stable α -adduct.



Scheme 121

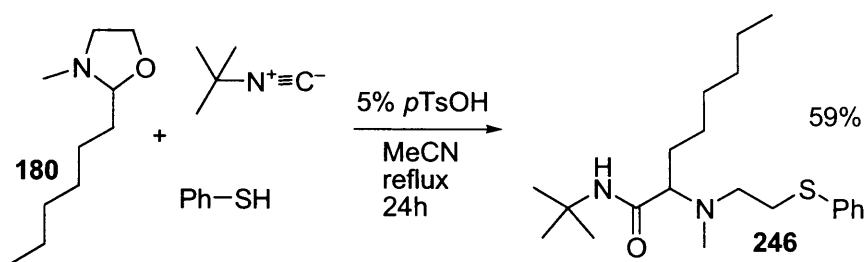
Thiobenzoic acid was the first alternative to be investigated, Even though this ambident nucleophile may still react either analogously to a carboxylic acid by the previously discussed mechanisms or by the above mentioned proton assisted direct attack on the cyclic imino ether intermediate **213**. Thiobenzoic acid has a pKa of 5.2 in DMSO,¹⁴³ which is significantly lower than benzoic acid (11.1 in DMSO).¹⁴⁴ Gratifyingly, when oxazolidine **179**, *tert*-butyl isocyanide and thiobenzoic acid were heated in the presence of 10 mol% *p*TsOH catalyst, *S*-{2-[(*tert*-Butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]-ethyl}thiobenzoate **245**, was isolated in a modest yield of 20% (Scheme 121). MeCN was chosen as a solvent since it had previously provided the best yield for exocyclic imino ether **217** formation (Scheme 117).



Scheme 121

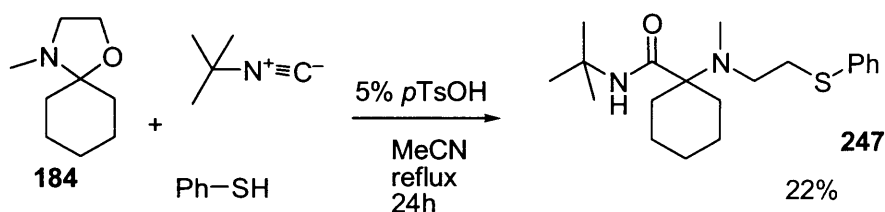
Extended reaction times led to no increase in yield. Use of thioacetic acid, sadly, led to a complex mixture presumably due to its lower stability compared with thiobenzoic acid.

The selection of thiophenol (pKa = 10.3 in DMSO)¹⁴⁵ as a simpler nucleophilic partner led to an improved yield of 59% when reacted with oxazolidine **180** and *tert*-butyl isocyanide (Scheme 122).



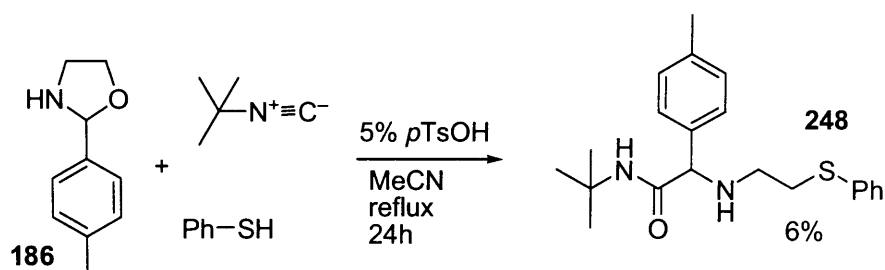
Scheme 122

This reaction was also found to be applicable to the ketone derived spirocyclic oxazolidine **184**, albeit in a lower yield of 22% (Scheme 123).



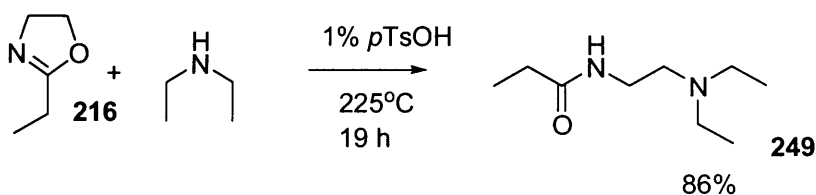
Scheme 123

The use of the ethanolamine derived *NH*-oxazolidine **186** resulted in an extremely low yield of 6% with no other isolated products (Scheme 124).



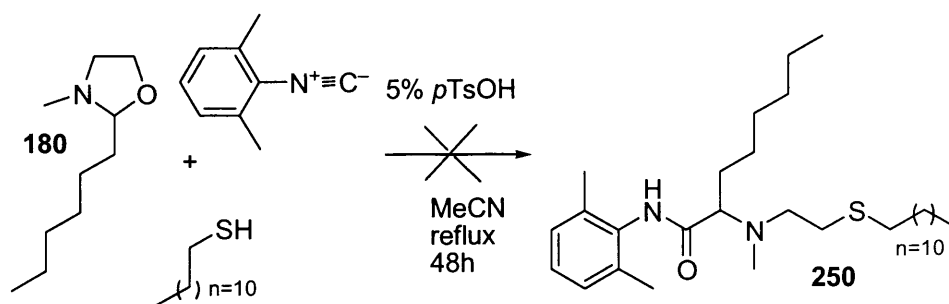
Scheme 124

This was possibly due to attack of the secondary amine starting material on the exocyclic imino ether intermediate, since Fazio has demonstrated that secondary amines can undergo *p*TsOH catalysed attack on oxazoline **216**, despite their high *p*K_a of ~ 44,¹⁴⁶ albeit at a significantly higher temperature (Scheme 125).¹⁴⁷



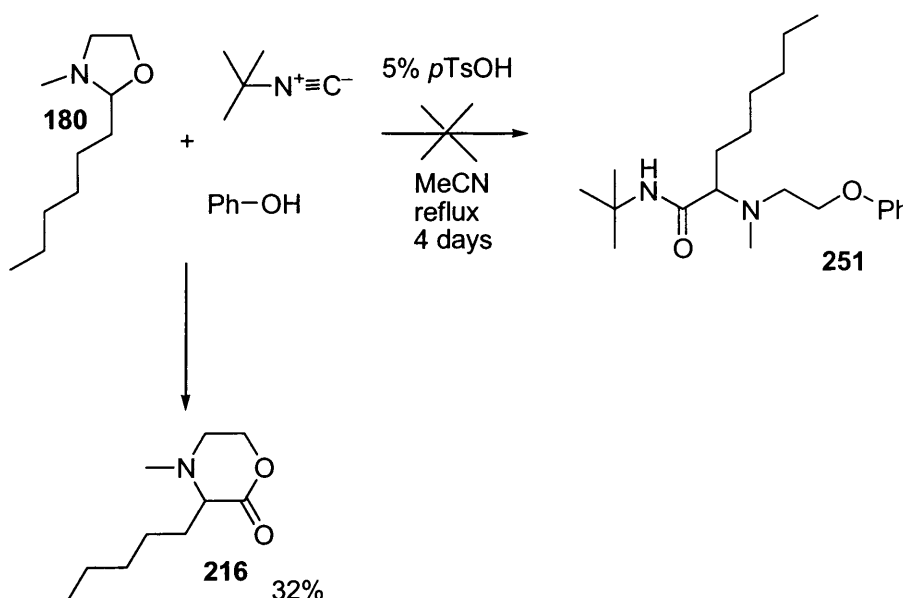
Scheme 125

When an aliphatic thiol – *n*-dodecanethiol was used in the place of thiophenol with *N*-alkyl oxazolidine **180** and 2,6-dimethylphenyl isocyanide, no expected product **250** was observed (Scheme 126), instead the exocyclic imino ether intermediate **217** was isolated in 75% yield (Scheme 126). This was thought to be due to the increased pK_a of ~17.0,¹⁴⁸ since the nucleophilic nature of the mercaptan should of course be similar to thiophenol.



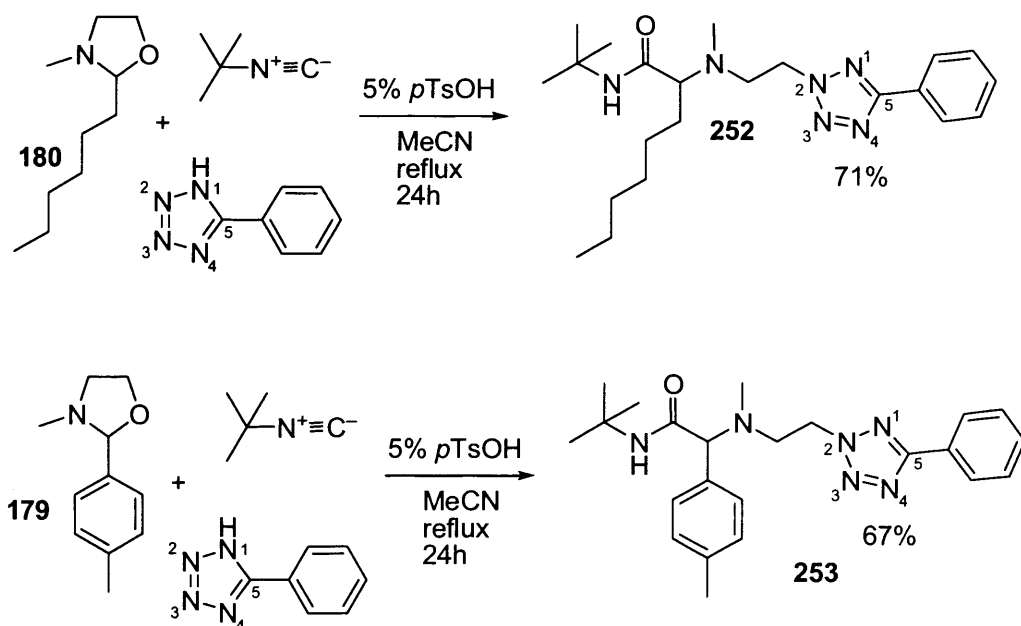
Scheme 126

Similarly, when phenol (pK_a = 18.0)¹⁴⁷ was applied to this reaction as a nucleophile, no anticipated product **251** was isolated, but instead only the morpholinone **216** in 32% yield (Scheme 127).



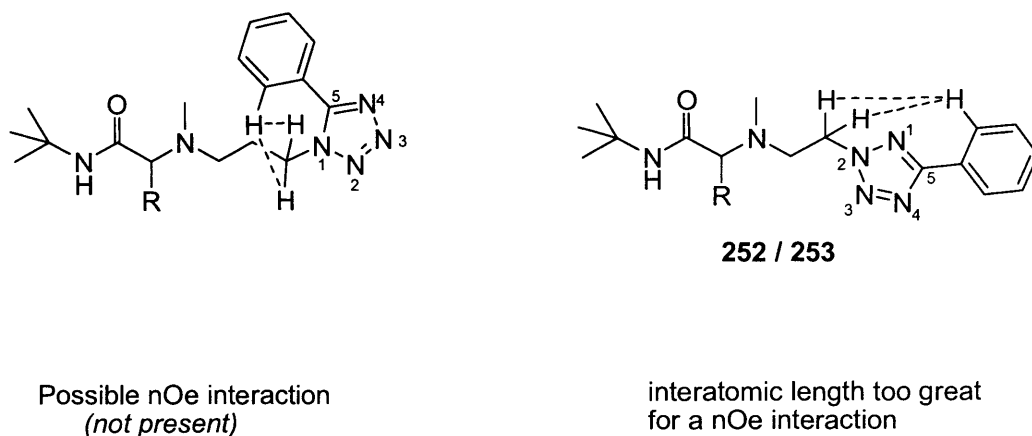
Scheme 127

The use of 5-phenyl-1*H*-tetrazole (pK_a ~ 8.2)¹⁴⁹ as a nucleophile gave a vastly higher yields of 71% and 67% of the multicomponent products **252** and **253** (Scheme 128).



Scheme 128

Interestingly, nuclear Overhauser effect studies show an absence of an nOe enhancement between the aryl-CH and the CH₂ adjacent to the tetrazole. This suggests that the regiochemistry of the tetrazole product is exclusively 2-5 substituted and not 1-5 (Scheme 129).



Scheme 129

No $^3J_{\text{CH}}$ coupling between the tetrazole-CH₂ and C=N is observed in the ^1H NMR HMBC spectrum, again suggesting exclusive 2-5 substitution.

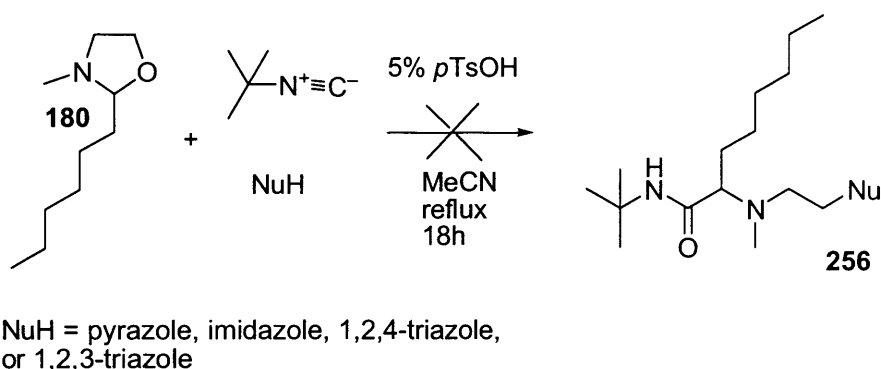
5-Phenyl-1*H*-tetrazole therefore attacks the exocyclic imino ether intermediate **213** exclusively *via* the tetrazole 2-position. The nitrogen at the 2-position possessing a lone pair in tautomer **255** is significantly less sterically shielded than the nitrogen

atom at the 1-position in tautomer **254** and thus would be expected to be more nucleophilic (Scheme 130).



Scheme 130

Initial investigations showed that pyrazole ($\text{pK}_a = 19.8$),¹⁴⁹ imidazole ($\text{pK}_a = 18.6$),¹⁴⁹ 1,2,4-triazole ($\text{pK}_a = 14.8$)¹⁴⁹ and 1,2,3-triazole ($\text{pK}_a = 13.9$)¹⁴⁹ did not give any expected multicomponent reaction products **256** as depicted in Scheme 131. Once again this is thought to be due to the excessively high pK_a 's of these potential nucleophiles.



Scheme 131

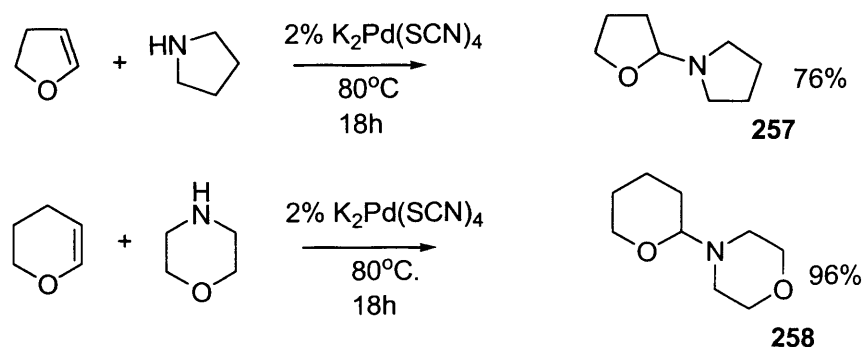
In summary, there appears to be a correlation between pK_a and efficacy as a nucleophile for $\text{S}_{\text{N}}2$ type attack of the exocyclic imino ether intermediate **213** as part of an IMCR. There is also a distinct preference for soft nucleophiles in this reaction. It is thought that hard nucleophiles are either attacking the nitrilium ion or the $\text{C}=\text{N}$ double bond and thus not giving stable products.

2.8 Bicyclic *N-O* Acetals as Substrates for IMCRs.

2.81 Preparation of Bicyclic *N-O* Acetals as Substrates for IMCRs.

The successful use of oxazolidines as substrates for an IMCR led to further investigation into the use of alternative *N-O* acetals with an exocyclic nitrogen atom. α -Amino-tetrahydrofuran and α -amino-tetrahydropyran rings may be simply produced in high yield by the addition of secondary amines to 2,3-dihydrofuran or 2,3-dihydropyran using $K_2Pd(SCN)_4$ as a catalyst (Scheme 132).¹⁵⁰

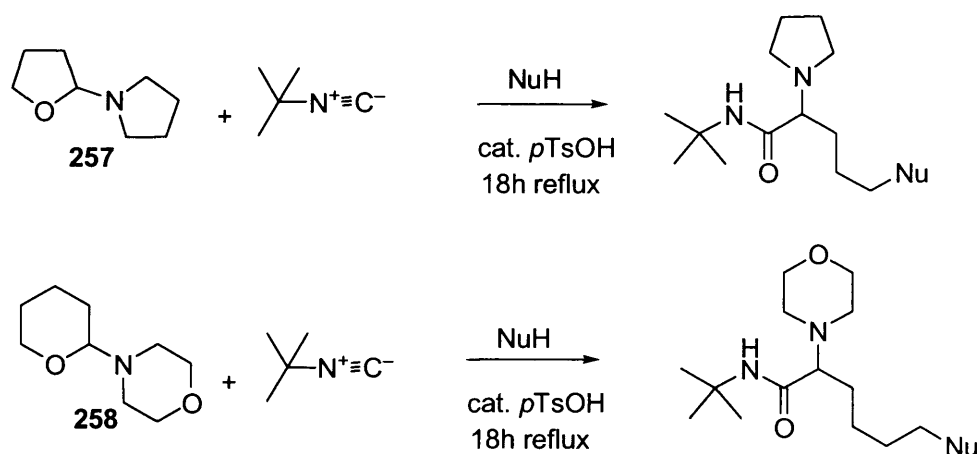
Thus, two representative bicyclic *N-O* acetals **257** and **258** were prepared using this methodology in order to provide starting materials for development of further isocyanide based multicomponent reactions (Scheme 133).



Scheme 132

2.82 Use of Bicyclic *N-O* Acetals in 3-CRs.

Since exocyclic *N-O* acetals have a similar functional group connectivity to *N*-alkyl oxazolidines, it was envisaged that they would have a similar reactivity profile under acidic conditions: ring opening to an iminium ion with a pendant hydroxyl group. With this in mind, the IMCRs between bicyclic *N-O* acetals **257** or **258** *tert*-butyl isocyanide and a nucleophile were attempted using the conditions previously developed for oxazolidine IMCRs (Scheme 133). The results of this preliminary experimental screen are shown in Table 14.



NuH = PhCOOH, 1*H*-phenyl tetrazole, PhSH

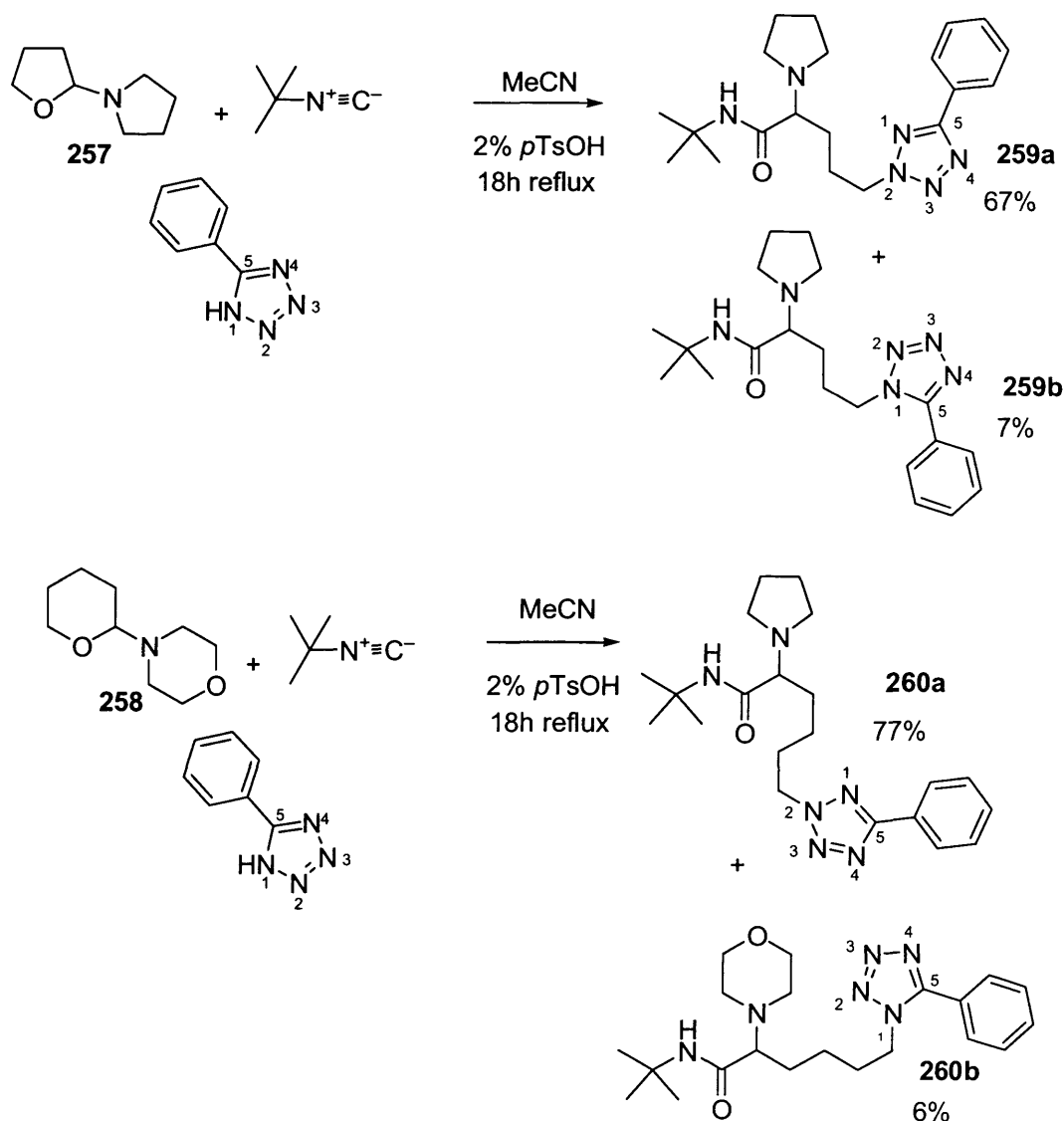
Scheme 133

Acetal	Nucleophile	Solvent	Time	Temp	<i>p</i> TsOH %	Yield	Product
257	PhCOOH	IPA	18h	reflux	2	0%	-
257	PhCOOH	MeOH	42h	r.t	2	0%	-
257	5-phenyl-1 <i>H</i> -tetrazole	MeCN	18h	reflux	10	74% ^A	259
257	PhSH	MeCN	18h	reflux	10	0%	-
258	PhCOOH	IPA	18h	reflux	2	0%	-
258	PhCOOH	MeOH	42h	r.t	2	0%	-
258	5-phenyl-1 <i>H</i> -tetrazole	MeCN	18h	reflux	10	83% ^B	260
258	PhSH	MeCN	18h	reflux	10	0%	-

^A= 10:1 ratio of 2-5 to 1-5 regioisomer, ^B= 15:1 ratio of 1-3 to 1-2 regioisomer.

Table 14. IMCRs with bicyclic *N*-*O* acetals & different nucleophiles.

Most curiously, and in total contrast to the oxazolidines, only 5-phenyl-1*H*-tetrazole was successful under the conditions previously demonstrated for oxazolidine IMCRs (Scheme 134). Moreover, unlike the case of the reaction between an *N*-alkyl oxazolidine **180**, an isocyanide and 5-phenyl-1*H*-tetrazole (Scheme 128) in which exclusive formation of 2,5-regioisomer was observed, mixtures of 10:1 and 15:1 respectively, of the 2,5-regioisomer to 1,5-regioisomer were isolated.



Scheme 134

This nucleophile was also seen in the preceding section to be by far the most effective of those investigated, but at the present time, no convincing explanations can be offered as to why benzoic acid and thiophenol were not successful in this reaction under the current conditions, despite the similar connectivity pattern of these bicyclic *N*-*O* acetals to *N*-alkyl oxazolidines.

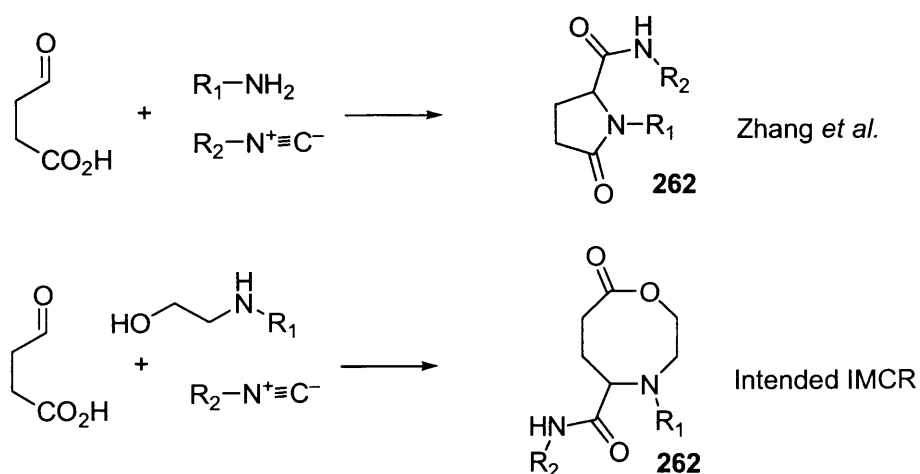
The unusual behaviour of the thiophenol and benzoic acid nucleophiles was not further investigated. This was principally due to the fact that the anticipated products were not of much biological interest for compound library generation, due to their long central four carbon chain rendering them far too conformationally flexible.

Our attention then turned to the development of novel IMCRs featuring the use of a bifunctional substrate as a key component in an ethanolamine based reaction, thereby introducing novel elements of structural diversity and reactivity.

2.91 IMCRs Using Bifunctional Aldehyde – Carboxylic Acids,

Ethanolamines, and Isocyanides.

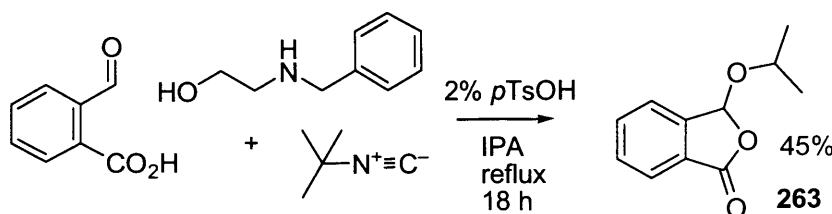
Thus far, the major drawback of the IMCR products described in this thesis is their lack of rigidity. The vast majority of biologically active molecules are more conformationally rigid, thus allowing them to fit in receptors in a lock and key manner. As previously discussed (*Section 1.522*), Gross *et al.* and later Zhang and co-workers have described the use of aldehyde-carboxylic acid tethered substrates for IMCRs, giving biologically relevant products.^{78,82} It was envisaged that this reaction may be extended through the use of an ethanolamine as the amine component (Scheme 135) in a similar manner to the way ethanolamine has been used to extend the Ugi reaction earlier in this work.



Scheme 135

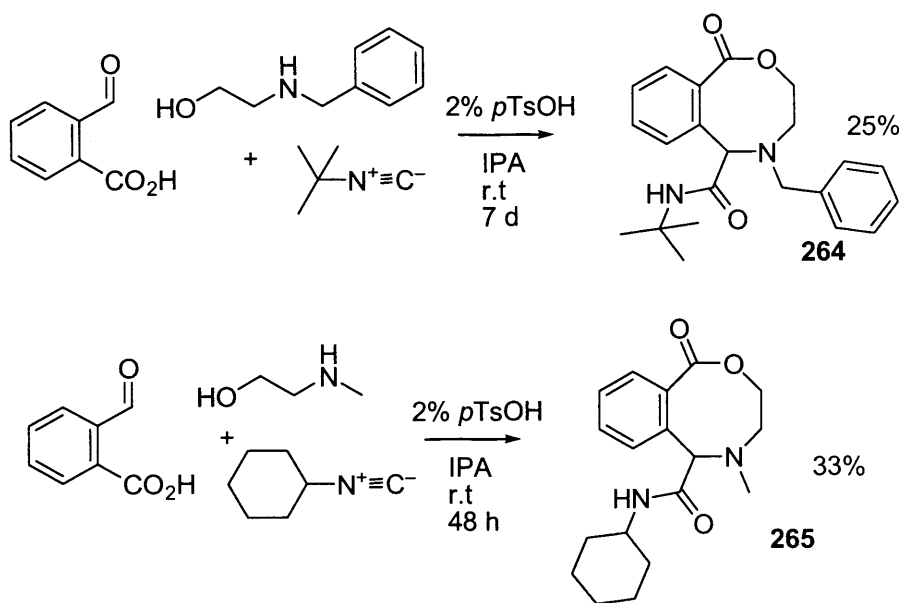
In order to investigate this reaction, 2-carboxybenzaldehyde was chosen as the bifunctional substrate with *N*-benzylaminoethanol and *tert*-butyl isocyanide. Initial conditions using IPA as solvent at reflux for 18 hours in the presence of 2 mol%

*p*TsOH were investigated. Interestingly, this led to incorporation of the isopropyl group from the alcohol to give of 3-isopropoxyisobenzofuran-1(3*H*)-one **263** in a reaction which did not involve the ethanolamine or isocyanide components (Scheme 136).



Scheme 136

Nevertheless, even though lowering the reaction temperature to room temperature led to considerably longer reaction times for this reaction, product **264** was isolated in 25% yield after 7 days (Scheme 137). This was however, considered a success since the reaction was now proven to be possible. Use of the less sterically demanding *N*-methylethanolamine with *tert*-butyl isocyanide resulted in shorter reaction times of 48 hours and an increased yield of 33%.

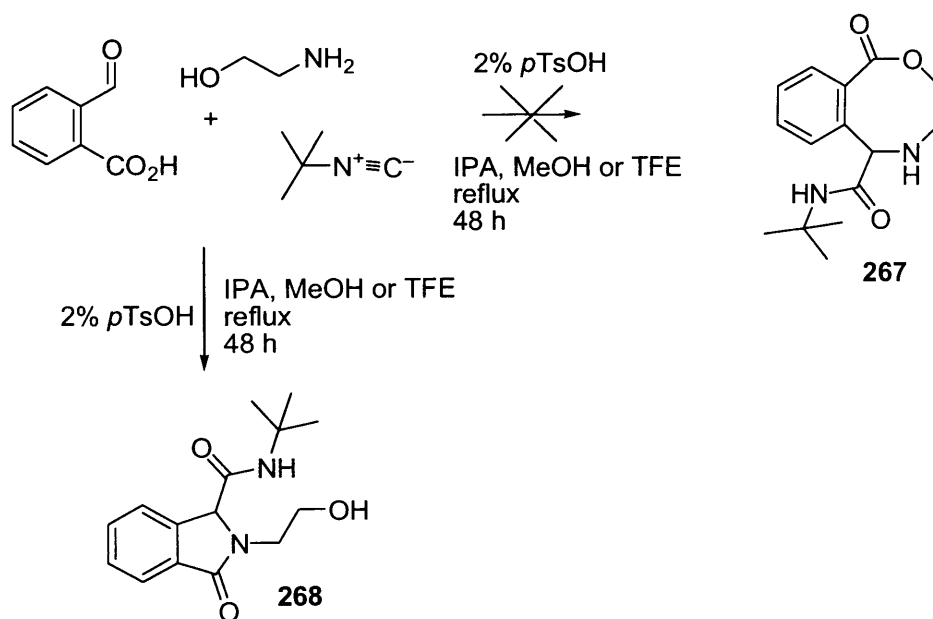


Scheme 137

Zhang and co-workers have demonstrated the use of ethanolamine with assorted bifunctional carbonyl-carboxylic acids including 2-carboxybenzaldehyde.⁸² They

only isolated the Ugi four centred, three component reaction product (U-4C-3CR). In the case of ethanolamine derived oxazolidines, the use of IPA at reflux led to the preference for an 8-membered *O*-acyl migration rather than the theoretically and energetically favoured 5-membered *N*-acyl migration. The reaction between 2-carboxybenzaldehyde, ethanolamine and an *tert*-butyl isocyanide results in similar intermediates and as such it was expected that the use of alternative reaction conditions may lead to isolation of an entirely different product **267** to that of Zhang *et al.*⁸²

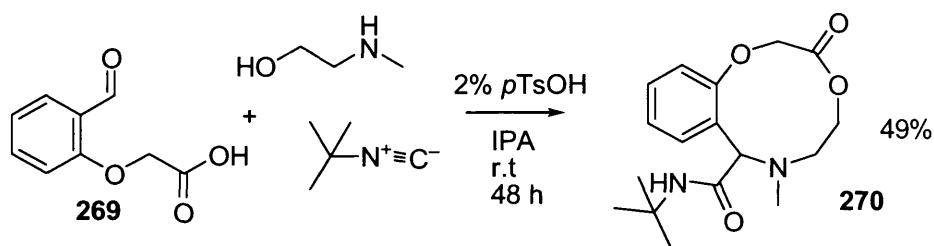
Sadly, the use of IPA at reflux with 2 mol% *p*TsOH merely led to detection of Zhang's Ugi type product **268** by ¹H NMR after 48 hours (Scheme 138). In similar fashion, use of MeOH and 2,2,2-trifluoroethanol at reflux led to no detection of the elusive desired product **267**.



Scheme 138

After the successful IMCRs using 2-carboxybenzaldehyde and *N*-substituted ethanolamines (Scheme 137), more complex bifunctionalised substrates which would require larger than 8-membered *N*-acyl migrations were investigated. The readily available 2-formylphenoxyacetic acid **269** must react *via* an entropically disfavoured

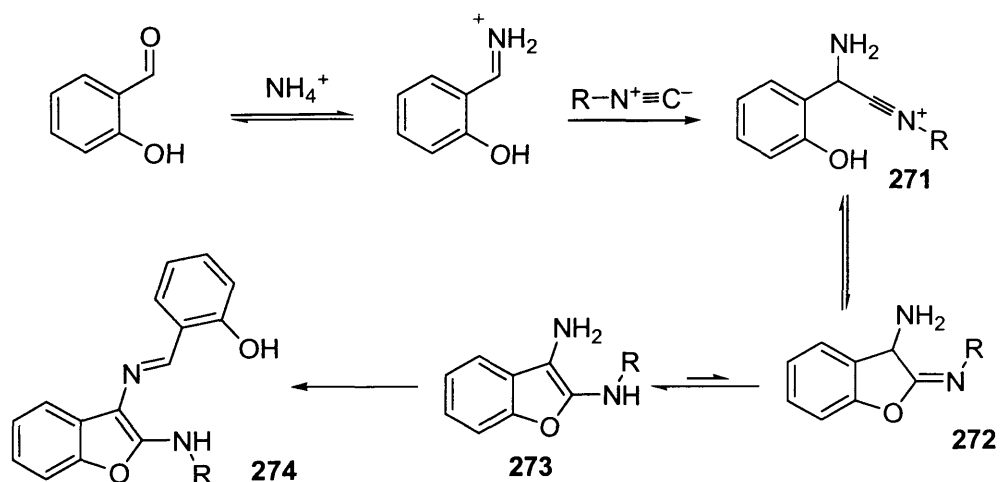
and transannularly strained 10-membered intramolecular *O*-acyl migration. It was therefore surprising when the relatively high yield of 49% was achieved after 48 hours (Scheme 139).



Scheme 139

2.92 IMCRs using Bifunctional Carbonyl-Hydroxyl Compounds.

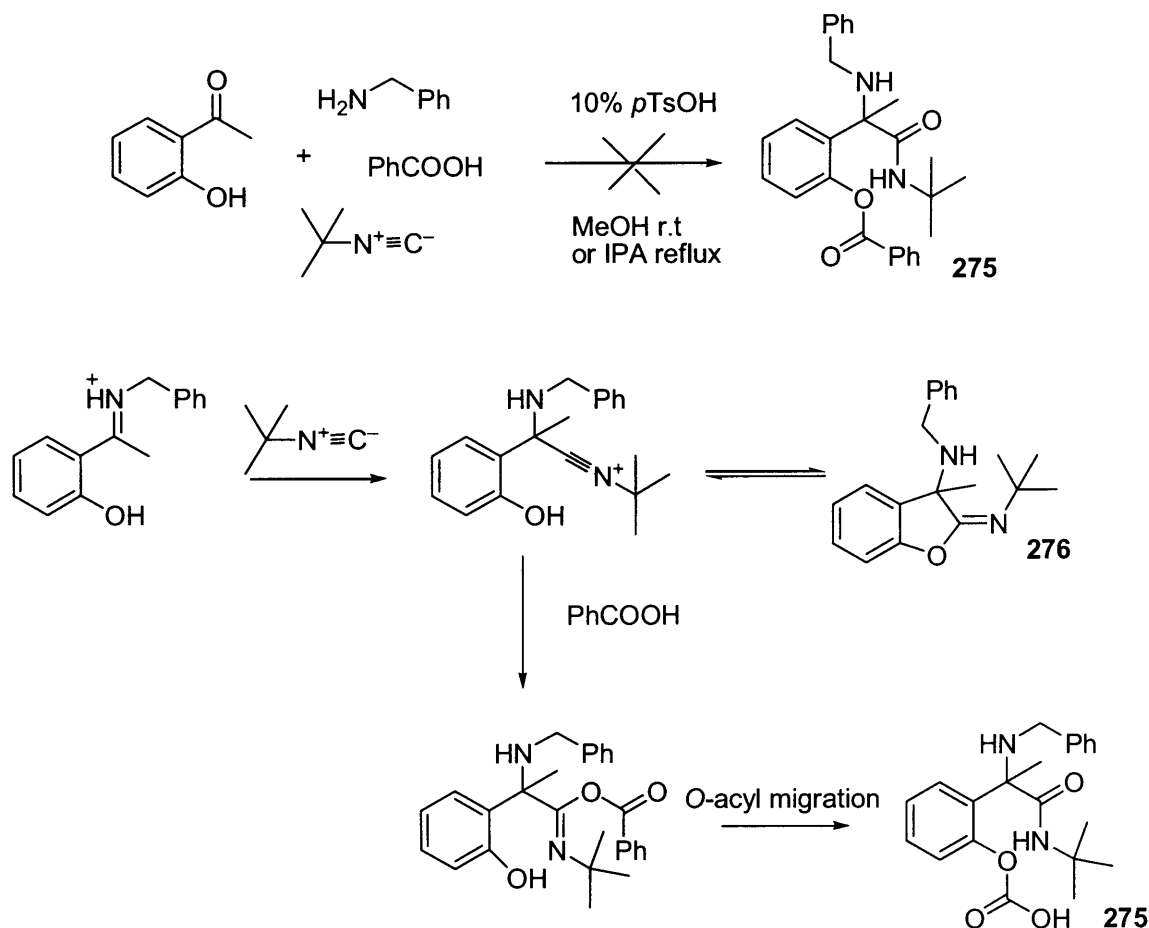
Marcaccini *et al.* have shown that the phenolic hydroxyl group of salicylaldehyde is sufficiently acidic to replace a carboxylic acid in an Ugi reaction with an isocyanide and ammonium formate (Scheme 140).¹⁵¹ In this reaction, the iminium ion **271** is attacked by the isocyanide with subsequent ring closure to an exocyclic imino ether **272**, which reacts further with a second molecule of salicylaldehyde to form the stable imine product **274**.



Scheme 140

We therefore elected to investigate the reaction of *o*-Hydroxyacetophenone with benzylamine, *tert*-butyl isocyanide and benzoic acid (Scheme 141). It was

anticipated that since the amine used in this case is primary, the exocyclic imino ether intermediate **276** will not react further with a second molecule of salicylaldehyde to give a stable product, but instead the benzoic acid nucleophile would become involved in a mechanism similar to that which has been previously encountered.



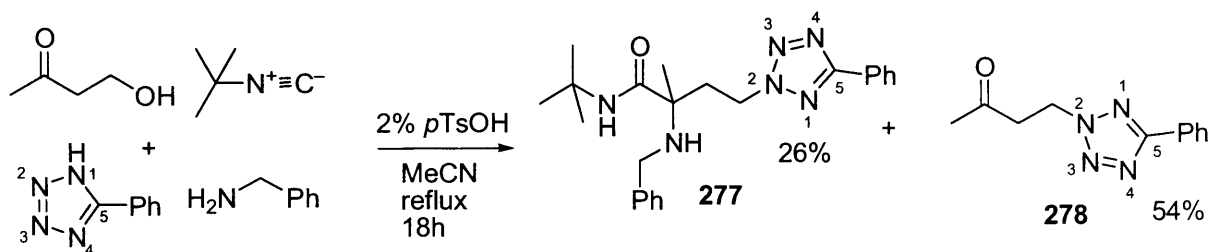
Scheme 141

However, disappointingly, despite promising indications from the crude ^1H NMR spectra, it was not possible to isolate pure products from this complex reaction mixture.

4-Hydroxy-2-butanone was then investigated since the exocyclic imino ether intermediate, in this case, would be able to be attacked by alternative nucleophiles to carboxylic acids unlike in the above example. It also should have the advantage of the exocyclic imino ether not forming the amino dihydrofuran type of structure **273** noted above where conjugation with the aromatic ring affords stability.

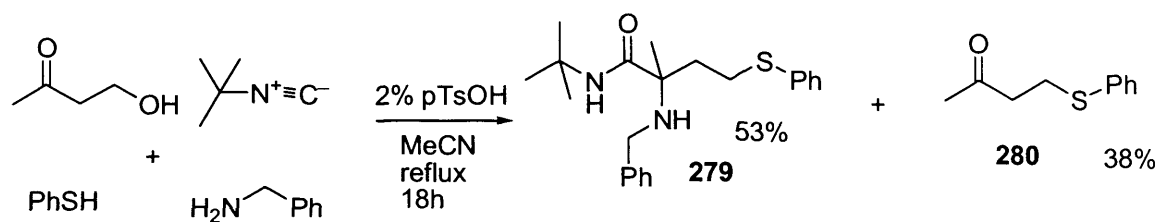
When 5-phenyl-1*H*-tetrazole was used as the nucleophilic component with 4-hydroxy-2-butanone, benzylamine and *tert*-butyl isocyanide in MeCN at reflux with 2 mol% *p*TsOH, an acceptable yield of 26 % of the 2-5 tetrazole regioisomer was isolated (Scheme 142).

The proton coupled ^{13}C spectrum shows a triplet (4.4 Hz $^3J_{\text{CH}}$) coupling to the *ortho* proton at 165.2 ppm. This indicates the presence of the 2-5 regioisomer, also indicated by the absence of a triplet of triplets at 165.2 for the 1-5 regioisomer in which $\text{C}=\text{N}$ would couple with the *ortho* proton and the $\text{N}-\text{CH}_2$. No $^3J_{\text{CH}}$ coupling between the $\text{N}-\text{CH}_2$ and $\text{C}=\text{N}$ is observed in the HMBC spectrum, again suggesting exclusive 2-5 substitution. The major constituent of the product mixture was 54% of 4-(5-phenyl-2*H*-tetrazol-2-yl)butan-2-one side product **278**. This was most probably formed by acid catalysed elimination of water from the 4-hydroxy-2-butanone starting material followed by Michael addition by the soft nucleophile, and explains the poor yield of expected product **277**.



Scheme 142

Similarly, when thiophenol was used as the nucleophile, the expected product **279** was isolated in 53% yield, together with 38% 4-(phenylthio)butan-2-one side product **280** (Scheme 143). Use of IPA as solvent in both cases gave lower yields of the desired products and higher levels of side product.



Scheme 143

Conclusions and Future Perspectives.

This present thesis has described the development of several simple and useful IMCRs. By the investigation of oxazolidines and their congeners, it has been demonstrated that an ethanolamine moiety may take part in an Ugi type reaction in a similar manner to the U-4C-3CR of homoserine **84**, whereby the hydroxyl group takes an active part in the reaction mechanism. Alternative nucleophiles to the ubiquitous carboxylic acid have also been shown to be applicable for IMCRs that react *via* an exocyclic imino ether intermediate **213**.

The potential for further investigation of these reactions lies both in the stereocontrol of the new chiral centre and in the exploration of further substrates. It seems likely that if a chiral amino alcohol is used then good stereochemical induction would be achieved in a similar manner to the Ugi reaction. The use of alternative five-membered saturated heterocycles would possibly lead to new and exciting structures. 1,3-Dithiolanes, 1,3-oxathiolanes, thiazolidines and 1,3-oxazinanes and also their antecedent bifunctional starting materials would all be worth investigating.

Part 3:

EXPERIMENTAL

3.1 General Experimental Procedures.

3.11 Solvents and Reagents.

Unless otherwise stated, all reactions were performed using oven dried glassware, which was cooled under a flow of nitrogen or argon prior to use.¹⁵² Benzene and DMSO were distilled from calcium hydride; THF, CH₂Cl₂, Et₂O, MeCN, toluene and *n*-hexane, were prepared as anhydrous, degassed solvents from an anhydrous engineering[®] zeolite drying apparatus. Methanol and ethanol were distilled from magnesium methoxide. Hexanes refers to light petroleum ether b.p. 60-80°C.¹⁵³ Anhydrous IPA was purchased from Sigma-Aldrich[®].

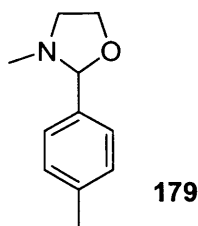
3.12 Data Collection.

Melting points were performed on a Reichert Thermovar hot stage apparatus and are uncorrected. Boiling points were measured during distillation and are uncorrected. Proton magnetic resonance (¹H NMR) spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer at 300K unless otherwise stated, and are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant *J* (Hz), assignment). The coupling constants are quoted to the nearest 0.1 Hz (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, m=multiplet, b=broad) and are reported as measured splittings on each individual resonance. The residual protic solvent CHCl₃ (δ_{H} = 7.26 ppm, s) DMSO (δ_{H} = 2.50 ppm, qn) and MeOH (δ_{H} = 3.30 ppm, q) were used as an internal reference. ¹³C spectra (¹³C NMR) were recorded at 75 MHz on a Bruker AMX300 spectrometer at 300K unless otherwise stated. The central reference of CDCl₃ (δ_{C} = 77.0 ppm, t), DMSO (D₆) (δ_{C} = 39.4 ppm, septuplet) or

MeOH (D₄) (δ_c = 49.0 ppm, septuplet) was used as an internal reference. Chemical shifts are reported to the nearest 0.1 ppm or 0.01 ppm in cases where adjacent peaks are less than 0.1 ppm apart. Infrared spectra were carried out on a Shimadzu FTIR – 8700 and are recorded as a KBr disc or as a neat oil in between NaCl disks. Only selected absorbencies (ν_{\max}) $>1400\text{ cm}^{-1}$ are reported with the exception of strong structurally important fingerprint region peaks ($1400\text{-}600\text{ cm}^{-1}$). Mass spectra and accurate mass measurements were recorded using a Micromass 70-SE magnetic sector spectrometer at the University College London Chemistry Department.

3.2 Experimental Procedures.

3-Methyl-2-*p*-tolyl-oxazolidine **179**.



2-(Methylamino)-ethanol (1.5 g / 1.61 ml, 20 mmol) and *p*-tolualdehyde (3.02 g, 20 mmol) were added sequentially in one portion to ethanol (20 ml) and stirred at r.t. for 1.5 h. The solvent was removed under reduced pressure and ethanol (10 ml) was added and then immediately removed under reduced pressure. The addition and evaporation of ethanol was repeated three times and then the product was dried under vacuum for 11 h to give crude 3-methyl-2-*p*-tolyl-oxazolidine **179** (3.6 g, 90 %) as a colourless oil, which was distilled under reduced pressure (96-98°C, 0.5 mm/Hg), (lit¹⁵⁴ = 67-68°C, 0.05 mm/Hg) to give 3-methyl-2-*p*-tolyl-oxazolidine **179** (2.9 g, 83 %).

^1H NMR (CDCl_3) δ 2.28 (3H, s, N- CH_3), 2.35 (3H, s, tolyl- CH_3), 2.70 (1H, dd, $J=9.1, 17.0$ Hz, N- $\text{CH}_\text{A}\text{CH}_\text{B}$), 3.30-3.36 (1H, m, N- $\text{CH}_\text{A}\text{CH}_\text{B}$), 3.99-4.14 (2H, m, O- CH_2), 4.62 (1H, s, *tert*-CH), 7.24 (2H, d, $J=17.1$ Hz, Ar), 7.33 (2H, d, $J=16.5$ Hz, Ar).

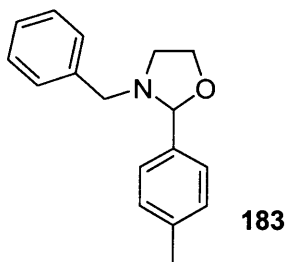
^{13}C NMR (CDCl_3) δ 21.3, 38.2, 54.7, 65.3, 98.3, 127.6, 129.0, 129.7, 129.8, 136.1, 138.5.

HRMS - (FAB (pos)) - calculated for $\text{C}_{11}\text{H}_{16}\text{NO}$: 178.12318, found 178.12330.

LRMS - (FAB (pos)) 154 (100), 178 (85, $\text{M}+\text{H}$), 155 (30), 177 (20), 179 (10), 156 (7).

IR (thin film) ν max- 3029, (aryl), 2994 (alkyl), 2955 (alkyl), 2897 (alkyl), 2816 (N- CH_3), 1701, 1690, 1604, 1456 cm^{-1} .

3-Benzyl-2-*p*-tolyl-oxazolidine **183**.



2-(Benzylamino)-ethanol (3.02 g, 20 mmol) and *p*-tolualdehyde (3.02 g, 20 mmol) were added sequentially in one portion to ethanol (5 ml) and stirred at r.t. for 1.5 h. The solvent was removed under reduced pressure and ethanol (10 ml) was added and then immediately removed under reduced pressure. The addition and evaporation of ethanol was repeated three times and the product was dried under vacuum for 24 h to give the crude oxazolidine **183** (5.1 g, 97 %) as a yellow oil. This was distilled under reduced pressure (137-140°C, 0.03 mm/Hg), (lit¹⁵⁵ = 129°C, 0.1 mm/Hg) to yield 3-benzyl-2-*p*-tolyl-oxazolidine **183** as a colourless oil (4.6 g, 91 %).

^1H NMR (CDCl_3) δ 2.46 (3H, s, tolyl- CH_3), 2.70-2.79 (1H, m, $\text{N-CH}_\text{A}\text{H}_\text{B}$), 3.21-3.28 (1H, m, $\text{N-CH}_\text{A}\text{H}_\text{B}$), 3.45 (1H, d, $J = 13.0$ Hz, $\text{Ar-CH}_\text{A}\text{H}_\text{B}$), 3.92 (1H, d, $J = 13.0$ Hz, $\text{Ar-CH}_\text{A}\text{H}_\text{B}$), 4.08-4.16 (2H, m, O-CH_2), 5.02 (1H, s, CH), 7.25-7.46 (9H, m, Ar).

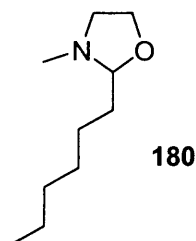
^{13}C NMR (CDCl_3) δ 21.4, 51.6, 56.3, 65.3, 96.8, 127.2, 127.9, 128.5, 128.8, 129.2, 136.8, 138.5, 139.0.

HRMS - (FAB (pos)) – calculated for $\text{C}_{17}\text{H}_{20}\text{NO}$: 254.15449, found 254.15465.

LRMS - (FAB (pos)) 254 (100, $\text{M}+\text{H}$), 253 (83), 162 (55), 253 (45), 255 (20), 152 (10).

IR (thin film) ν max- 3026, (aryl), 2952 (alkyl), 2921 (alkyl), 2885 (alkyl), 1698, 1498, 1454 cm^{-1} .

2-Hexyl-3-methyl-oxazolidine 180.



1-Heptanal (20.0 g, 0.174 mol) and 2-(methyamino)-ethanol (13.1 g, 0.174 mol) were added to anhydrous benzene (125 ml) and heated under an atmosphere of nitrogen at 80°C with iodine (10 mg, 0.04 mmol). The water was azeotropically removed using a Dean and Stark apparatus for 1.5 h. Excess solvent was removed under reduced pressure and the crude oxazolidine **180** (28.6 g) was distilled under reduced pressure ($67\text{--}69^\circ\text{C}$, 3 mm/Hg), (lit¹⁵⁶ = 103°C , 20 mm/Hg) to yield 2-hexyl-3-methyl-oxazolidine **180** as a colourless oil (21.9 g, 73 %).

^1H NMR (CDCl_3) δ 0.73 (3H, t, $J = 7.2$ Hz, CH_3), 1.23-1.30 (10H, m, $(\text{CH}_2)_5$), 2.19 (3H, s, N-CH_3), 2.45 (1H, dd, $J = 9.5, 8.3$ Hz, $\text{N-CH}_\text{A}\text{CH}_\text{B}$), 3.00-3.08 (1H, m, $\text{N-CH}_\text{A}\text{CH}_\text{B}$), 3.65-3.72 (3H, m, O-CH_2 & CH).

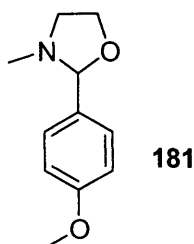
^{13}C NMR (CDCl_3) δ 13.9, 22.5, 24.8, 29.3, 21.7, 33.2, 38.7, 54.7, 63.9, 97.2.

HRMS - (FAB (pos)) - calculated for $\text{C}_{10}\text{H}_{21}\text{NO}$: 172.17013, found 172.16977.

LRMS - (FAB (pos)) 154 (100), 172 (92, $\text{M}+\text{H}$), 155 (30), 170 (28), 156 (7).

IR (thin film) ν max- 2957 (alkyl), 2930 (alkyl), 2856 (alkyl), 2797 ($\text{N}-\text{CH}_3$), 1467, 1456 cm^{-1} .

2-(4-Methoxy-phenyl)-3-methyl-oxazolidine **181**.



2-(Methylamino)-ethanol (3.8 g, 50 mmol) and *p*-anisaldehyde (6.8 g, 50 mmol) were added to ethanol (10 ml) and stirred at r.t. for 0.5 h. Excess solvent was removed under reduced pressure and ethanol (10 ml) was added and then immediately removed under reduced pressure. The addition and evaporation of ethanol was repeated three times and the product was dried under vacuum for 12 h to give the crude oxazolidine **181** (9.1 g) as colourless oil. The crude oxazolidine **181** was distilled under reduced pressure ($94\text{--}97^\circ\text{C}$, 0.03 mm/Hg), (lit¹⁵⁷ = $133\text{--}136^\circ\text{C}$, 3 mm/Hg) to yield 2-(4-methoxy-phenyl)-3-methyl-oxazolidine **181** as a colourless oil (7.4 g, 77 %).

^1H NMR (CDCl_3) δ 2.20 (3H, s, $\text{N}-\text{CH}_3$), 2.59-2.62 (1H, m, $\text{N}-\text{CH}_\text{A}\text{H}_\text{B}$), 3.25-3.29 (1H, m, $\text{N}-\text{CH}_\text{A}\text{H}_\text{B}$), 3.77 (3H, s, OMe), 3.94-4.06 (2H, m, $\text{O}-\text{CH}_2$), 4.53 (1H, s, CH), 6.87 (2H, d, $J = 8.7\text{ Hz}$, Ar), 7.36 (2H, d, $J = 8.7\text{ Hz}$, Ar).

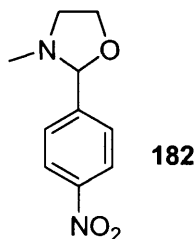
^{13}C NMR (CDCl_3) δ 38.0, 54.7, 55.2, 65.2, 98.0, 113.2, 129.2, 131.5, 160.1.

HRMS - (CI (pos) methane) - calculated for $\text{C}_{11}\text{H}_{12}\text{NO}$: 194.11810, found 194.11829.

LRMS - (CI (pos) methane) 135(100), 194 (58), 210 (53, M+CH₄), 86 (52), 192 (52), 137 (13).

IR (thin film) ν max- 2963 (alkyl), 2897 (alkyl), 2847 (alkyl), 2801 (N-CH₃), 1603, 1515 cm⁻¹

3-Methyl-2-(4-nitro-phenyl)-oxazolidine 182.



p-Nitrobenzaldehyde (7.6 g, 5 mmol) and 2-(methylamino)-ethanol (3.8 g, 5 mmol) were added to ethanol (10 ml) and stirred at r.t. for 30 mins. Excess solvent was removed under reduced pressure, and ethanol (10 ml) was then added and immediately removed under reduced pressure. The addition and evaporation of ethanol was repeated three times and the residue was dried under vacuum for 24 h to yield the crude oxazolidine **182** (10.2 g) as an orange oil. Distillation under reduced pressure (121-122°C, 0.02 mm/Hg), (lit¹⁵⁸= 118-119°C, 0.045 mm/Hg) gave 3-methyl-2-(4-nitro-phenyl)-oxazolidine **182** as an orange oil (6.3 g, 60 %). This was then triturated with petrol to give colourless prisms (6.1 g, 58 %), (m.p. = 31-34 °C), (lit¹⁵⁹= 31-32°C, from petrol).

¹H NMR (CDCl₃) δ 2.29 (3H, s, N-CH₃), 2.72 (1H, dd, J= 17.5, 8.1 Hz, N-CH_ACH_B), 3.20-3.26 (1H, m, N-CH_ACH_B), 4.01 (2H, dd, J= 7.5, 5.1 Hz, O-CH₂), 4.78 (1H, s, CH), 7.60 (2H, d, J= 8.5 Hz, Ar), 8.02 (2H, d, J= 8.5 Hz, Ar).

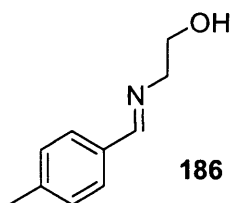
¹³C NMR (CDCl₃) δ 38.7, 54.4, 65.5, 97.0, 123.4, 124.2, 128.5, 130.4, 146.9, 148.2.

HRMS - (EI) - calculated for C₁₀H₁₂N₂O₃: 208.08479, found 208.08538.

LRMS - (EI) 86 (100), 92 (41), 150 (24), 207 (23), 104 (19), 161 (17).

IR (KBr Disc) ν max- 2955 (alkyl), 2895 (alkyl), 2800 (N-CH₃), 1609, 1522 (nitro), 1452, 1348 (nitro) cm⁻¹.

(*E*)-2-[(4-Methyl-benzylidene)-amino]-ethanol **186**.



p-Tolualdehyde (9.8 g, 82 mmol) and ethanolamine (5.0 g, 82 mmol) were added to ethanol (40 ml) and stirred at r.t. for 30 mins. The solvent was removed under reduced pressure, and ethanol (10 ml) was then added and immediately removed under reduced pressure. The addition and evaporation of ethanol was repeated three times and the residue was dried under vacuum for 24 h to yield the crude oxazolidine **186** as a white solid. Recrystallisation from EtOAc gave (*E*)-2-[(4-Methyl-benzylidene)-amino]-ethanol **186** (11.9 g, 89 %), as colourless needles (m.p. = 45-46°C), (lit¹⁶⁰ = 67-69°C, from benzene).

¹H NMR (CDCl₃) δ 2.19 (3H, s, tolyl-CH₃), 2.91 (1H, bs, OH), 3.70 (2H, t, J = 4.9 Hz, N-CH₂), 3.81 (2H, t, J = 4.8 Hz, O-CH₂), 7.17 (2H, d, J = 8.0 Hz, Ar), 7.57 (2H, d, J = 8.0 Hz, Ar), 8.15 (1H, s, N=CH).

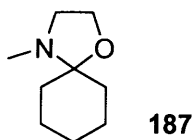
¹³C NMR (CDCl₃) δ 21.5, 62.4, 63.3, 128.2, 129.4, 133.3, 141.2, 163.1.

HRMS - (EI) - calculated for C₁₀H₁₃NO: 163.09971, found 163.10024.

LRMS - (EI) 86 (100), 92 (41), 150 (24), 207 (23), 104 (19), 161 (17).

IR (KBr disc) ν max- 3215 br (OH), 3028 (aryl), 2928 (alkyl), 2850 (alkyl), 1643 (C=N), 1607, 1569, 1408 cm⁻¹.

4-Methyl-1-oxa-4-aza-spiro[4.5]decane **187**.



Cyclohexanone (12.8 g, 0.13 mol), 2-(methylamino)ethanol (10 g, 0.13 mol) and iodine (10 mg, 0.04 mmol) were added to anhydrous benzene (100 ml). Water was azeotropically removed using Dean and Stark apparatus for 2.5 h. Excess solvent was removed under reduced pressure and the crude oxazolidine **187** (19.6 g) was distilled under reduced pressure (88-89°C, 20 mm/Hg), (lit¹⁶¹ = 89-92°C, 16 mm/Hg) to yield 4-methyl-1-oxa-4-aza-spiro[4.5]decane **187** as a colourless oil (17.4 g, 86 %).

¹H NMR (CDCl₃) δ 1.13-1.17 (1H, m, cy), 1.33-1.76 (9H, m, cy), 2.30 (3H, s, N-CH₃), 3.00 (2H, ddd, J = 6.6, 4.2, 2.5 Hz, N-CH_ACH_B), 3.82 (2H, ddd, J = 6.6, 4.4, 2.3 Hz, O-CH_AH_B).

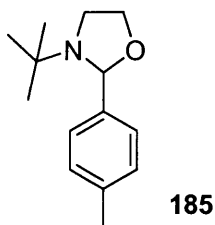
¹³C NMR (CDCl₃) δ 23.5, 25.6, 27.0, 32.3, 36.1, 42.0, 52.9, 62.5, 95.7.

HRMS - (EI) - calculated for C₉H₁₇NO: 155.13101, found 155.13121.

LRMS - (EI) 112 (100), 107 (78), 89 (40), 88 (33), 154 (23), 155 (20, m⁺).

IR (thin film) ν max- 2934 (alkyl), 2860 (alkyl), 2791 (N-CH₃), 1716, 1475, 1449 cm⁻¹.

3-tert-Butyl-2-p-tolyl-oxazolidine 185.



2-(tert-Butylamino)-ethanol (5.86 g, 50 mmol), *p*-tolualdehyde (7.55 g, 50 mmol) and iodine (5 mg, 0.02 mmol) were added to anhydrous benzene (50 ml). Water was azeotropically removed using Dean and Stark apparatus for 4 h. Excess solvent was

removed under reduced pressure and the residue was purified by distillation under reduced pressure (74-78°C, 0.02 mm/Hg) to give *3-tert-butyl-2-p-tolyl-oxazolidine* **185** as a colourless oil (7.0 g, 64 %).

¹H NMR (CDCl₃) δ 1.14 (9H, s, *t*-Bu), 2.34 (3H, s, tolyl-CH₃), 3.02-3.07 (1H, m, N-CH_A), 3.14-3.18 (1H, m, N-CH_B), 3.78-3.86 (2H, m, O-CH_AH_B), 5.65 (1H, s, CH), 7.16 (2H, d, *J* = 7.9 Hz, Ar). 7.46 (2H, d, *J* = 7.9 Hz, Ar).

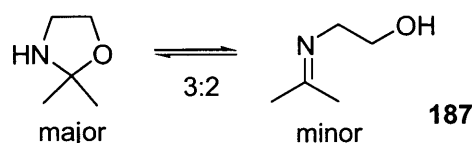
¹³C NMR (CDCl₃) δ 21.5, 27.9, 46.3, 53.5, 64.9, 91.4, 127.0, 129.6, 137.3, 140.6.

HRMS - (ES (pos)) - calculated for C₁₄H₂₂NO: 220.17014, found 220.17014.

LRMS - (ES (pos)) 220 (100, M+H), 176 (17), 164 (8), 221 (7), 175 (4), 201 (3).

IR (thin film) ν max- 2971 (alkyl), 2870 (alkyl), 1605, 1512, 1473 cm⁻¹.

2,2-Dimethyl-oxazolidine / 2-(propan-2-ylideneamino)ethanol **187**.



This compound was prepared according to a previously reported literature procedure.¹²²

To a solution of ethanolamine (10 g, 0.16 mol), in CH₂Cl₂ (100 ml) was added anhydrous potassium carbonate (15 g) and then acetone (18 ml, 0.24 mol) in one portion. The mixture was stirred under an atmosphere of nitrogen for 6 h at r.t. The suspension was filtered and the filtrate was evaporated under reduced pressure at 20°C. Distillation under reduced pressure (55-58°C, 80 mm/Hg), (lit¹²² = 75.5-76°C, 22 mm/Hg) gave 2,2-dimethyl-oxazolidine / 2-(propan-2-ylideneamino)ethanol as a colourless oil (12.9 g, 80 %).

¹H NMR (CDCl₃) (*two tautomers 3:2 ratio*) δ 1.32 (6H major, s, (CH₃)₂), 1.82 (3H minor, s, CH₃), 1.99 (3H minor, t, *J* = 1.5 Hz, CH₃), 2.80 (2H major, t, *J* = 5.2 Hz, N-

CH_ACH_B), 3.15 (2H minor, t, J= 6.7 Hz, N-CH₂), 3.27 (1H minor, bt, J= 4.6 Hz, OH), 3.57 (2H major, t, J= 5.2 Hz, O-CH_ACH_B), 3.71 (2H minor, t, J= 6.7 Hz, O-CH₂), 3.78 (1H major, t, J= 5.2 Hz, NH).

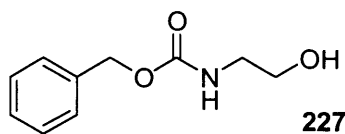
¹³C NMR (CDCl₃) δ 19.2, 26.2, 28.9, 43.7, 45.9, 63.6, 65.0, 94.8, 169.9.

HRMS - (CI (pos) methane) - calculated for C₅H₁₂NO: 102.09188, found 102.09166.

LRMS - (CI (pos) methane) 102 (100, M+H), 86 (79), 84 (52), 100 (10), 85 (9), 91 (5).

IR (thin film) ν max- 3358 br, 3296 br, 2935 (alkyl), 2869 (alkyl), 1665 (C=N), 1600 (NH), 1447 cm⁻¹

Benzyl 2-hydroxyethylcarbamate **227**.

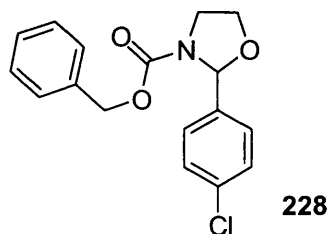


This compound was prepared according to a previously reported literature procedure.¹³²

To a solution of ethanolamine (15.3 g, 0.25 mol) in THF (133 ml) and water (266 ml), sodium bicarbonate (42 g) and then benzyl chloroformate (40.5 g, 0.24 mol) were added in one portion at 0°C and then vigorously stirred for 12 h at r.t. The suspension was filtered, and the THF layer was separated. Diethyl ether (50 ml) was added to the aqueous layer and stirred for 10 mins. The organic layer was then separated and the combined organic phases were combined, dried (MgSO₄) and then filtered. Concentration of the organic liquor under reduced pressure yielded benzyl 2-hydroxyethylcarbamate **227** as a white solid (21.5 g 44 %), (m.p. = 60-61°C), (lit¹⁶²= 62-62.5°C, from diethyl ether) of sufficient purity to be used directly in the next stage without further manipulation.

Spectroscopic data was identical to that previously reported.¹³²

Benzyl 2-(4-chlorophenyl)oxazolidine-3-carboxylate 228.



Benzyl 2-hydroxyethylcarbamate **227** (10.0 g, 51 mmol), *p*-chlorobenzaldehyde (7.2g, 51 mmol) and iodine (10 mg, 0.04 mmol) were added to toluene (100 ml) and heated at reflux using Dean and Stark water removal apparatus for 24 h. Excess solvent was removed under reduced pressure to yield a crude white solid which was recrystallised from EtOAc to give *benzyl 2-(4-chlorophenyl)oxazolidine-3-carboxylate 228* (9.75 g, 60 %), as colourless plates (m.p. = 53-55°C).

¹H NMR (CDCl₃) δ 3.54-3.62 (1H, m, N-CH_ACH_B), 3.85-3.98 (1H, m, N-CH_ACH_B), 4.01-4.4.14 (2H, m, O-CH₂), 5.12 (2H, s, Ar-CH₂), 6.98-7.50 (9H, m, Ar).

¹³C NMR (CDCl₃) δ 45.2, 65.9, 67.4, 88.7, 128.0, 128.2, 128.5, 128.6, 128.8, 134. 7, 136.1, 137.7, 153.8.

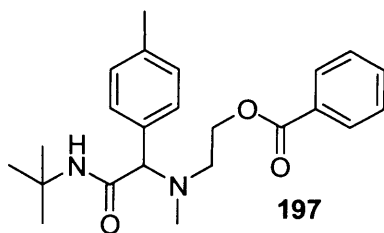
HRMS - (CI (pos - Methane)) - Measured (M+H) = 318.08914, theoretical (M+H) = 318.08969.

LRMS – (CI (pos - Methane)) 91 (100), 92 (75), 93 (67), 119(66), 89 (63), 117 (60).

IR (KBr Disc) ν max- 2924 (alkyl), 2855 (alkyl), 1713 (C=O), 1458, 1427, 1412 cm⁻¹.

¹.

2-[(tert-Butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]ethyl benzoate 197.



Method A

3-Methyl-2-*p*-tolyl-oxazolidine **179** (355 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μ l, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of nitrogen for 18 h. Excess solvent was removed under reduced pressure and the residue was purified by column chromatography (4:1 hexanes:EtOAc) to give 2-[(*tert*-butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]ethyl benzoate **197** (509 mg, 66 %) as a colourless oil. R.f = 0.23 (2:1 hexanes:EtOAc).

Method B

3-Methyl-2-*p*-tolyl-oxazolidine **179** (355 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *tert*-butyl isocyanide (166 mg / 226 μ l, 2 mmol) and *p*TsOH (38 mg, 0.2 mmol) were added to anhydrous THF (5 ml) and heated at reflux for 23 h. Excess solvent was removed under reduced pressure and the residue was purified by column chromatography (4:1 hexanes:EtOAc) to yield 2-[(*tert*-butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]ethyl benzoate **197** as a pale yellow oil (426 mg, 56 %).

Method C

3-Methyl-2-*p*-tolyl-oxazolidine **179** (355 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *tert*-butyl isocyanide (166 mg, 2 mmol) and *p*TsOH (38 mg, 0.2 mmol) were added to CH₂Cl₂ (3 ml) and heated to in a CEM[®] monomode microwave reactor for 20 minutes at 100°C. Excess solvent was removed under reduced pressure and the

crude product was purified by column chromatography (4:1 hexanes:EtOAc) to yield the title compound **197** as a pale yellow oil (379 mg, 50 %).

¹H NMR (CDCl₃) δ 1.27 (9H, s, *t*-Bu), 2.27 (3H, s, tolyl-CH₃), 2.34 (3H, s, N-CH₃), 2.67-2.88 (2H, m, N-CH₂), 4.00 (1H, s, CH), 4.33-4.65 (2H, m, O-CH₂), 6.93 (1H, bs, NH), 7.05-7.60 (9H, m, Ar).

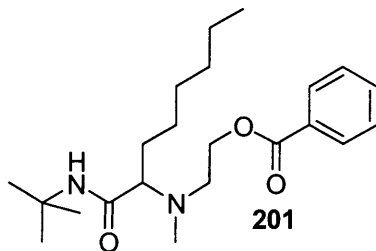
¹³C NMR (CDCl₃) δ 21.1, 28.6, 40.5, 50.7, 53.5, 62.4, 75.6, 128.4, 129.0, 129.2, 129.7, 130.1, 132.9, 133.1, 137.8, 166.5, 170.8.

HRMS - (FAB (pos)) - calculated for C₂₃H₃₁N₂O₃: 411.26475, found 411.26357.

LRMS - (FAB (pos)) 310 (100), 411 (60, M+H), 311 (35), 409 (22), 412 (17), 410 (8).

IR (thin film) ν max- 3400-3100 br (NH), 2928 (alkyl), 1718 (C=O), 1665 (C=O), 1604, 1514 (NH) cm⁻¹.

2-[(*tert*-Butylcarbamoyl-heptyl)methyl-amino]ethyl benzoate **201**.



Method A

2-Hexyl-3-methyl-oxazolidine **180** (343 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μl, 2 mmol) were added to anhydrous MeCN (5 ml) heated at reflux under an atmosphere of nitrogen for 21 h. Excess solvent was removed under reduced pressure and the residue was purified by column chromatography (4:1 hexanes:EtOAc) to yield 2-[(*tert*-butylcarbamoyl-heptyl)methyl-amino]ethyl benzoate **201** (599 mg, 80 %) as a colourless oil. R.f. = 0.34 (2:1 hexanes:EtOAc).

Method B

2-(Methylamino)-ethanol (161 μ l, 2 mmol), 1-heptanal (279 μ l, 2 mmol), benzoic acid (244 mg, 2 mmol) and *p*TsOH (8 mg, 0.04 mmol) were added to anhydrous IPA (2 ml), *tert*-Butyl isocyanide (166 mg / 226 μ l, 2 mmol) was then added and the mixture refluxed for 17h. Excess solvent was removed under reduced pressure and the residue was purified by column chromatography (4:1 hexanes:EtOAc) to give 2-*[(tert-butylcarbamoyl-heptyl)methyl-amino]ethyl benzoate* **201** (515 mg, 68 %) as a colourless oil.

¹H NMR (CDCl₃) δ 0.74 (3H, t, *J* = 6.9 Hz, CH₃), 1.16 (9H, s, *t*-Bu), 1.17-1.41 (6H, m, CH₂) 1.44-1.59 (2H, m, CH₂), 1.62-1.77 (2H, m, CH₂), 2.23 (3H, s, N-CH₃), 2.77-2.87 (3H, m, N-CH₂ and CH), 4.32-4.47 (2H, m, CH₂-O), 6.62 (1H, bs, NH), 7.40 (2H, t, *J* = 7.8 Hz, Ar), 7.53 (1H, t, *J* = 7.8 Hz, Ar), 8.00 (2H, d, *J* = 7.8 Hz, Ar).

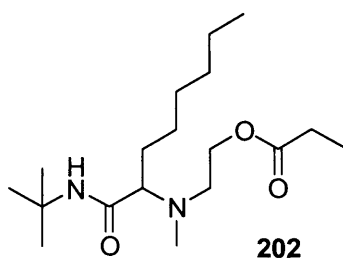
¹³C NMR (CDCl₃) δ 14.0, 22.5, 27.2, 27.4, 28.6, 29.5, 31.6, 38.3, 50.2, 53.7, 62.7, 68.9, 128.3, 129.5, 130.0, 133.0, 166.4, 172.2.

HRMS - (FAB (pos)) - calculated for C₂₂H₃₇N₂O₃: 377.28040, found 377.28061.

LRMS - (FAB (pos)) 276 (100), 377 (74, M+H), 277 (18), 378 (18), 154 (8), 375 (5).

IR (thin film) ν max- 3365 br (NH), 3026 (aryl), 2948 (alkyl), 2926 (alkyl), 2856 (alkyl), 1724 (C=O), 1674 (C=O), 1506 (NH), 1452 cm⁻¹.

2-*[(tert-Butylcarbamoyl-heptyl)methyl-amino]ethyl propionate* **202**.



2-Hexyl-3-methyl-oxazolidine **180** (343 mg, 2 mmol), propionic acid (149 μ l, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μ l, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of nitrogen for 21 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1 hexanes:EtOAc) to give 2-[(*tert*-butylcarbamoyl-heptyl)methyl-amino]ethyl propionate **202** (537 mg, 78 % as a colourless oil. R.f. = 0.21 (2:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 0.77 (3H, t, *J* = 6.6 Hz, heptyl-CH₃), 1.05 (3H, t, *J* = 7.5 Hz, propyl-CH₃), 1.13-1.23 (6H, m, CH₂), 1.25 (9H, s, *t*-Bu), 1.39-1.54 (2H, m, CH₂), 1.60-1.72 (2H, m, CH₂), 2.19 (3H, s, N-CH₃), 2.25 (2H, q, *J* = 7.5 Hz, C=O-CH₂), 2.53-2.71 (2H, m, N-CH₂), 2.77 (1H, dd, *J* = 7.3, 5.3 Hz, CH), 4.04 (2H, t, *J* = 6.5 Hz, O-CH₂), 6.78 (1H, bs, NH).

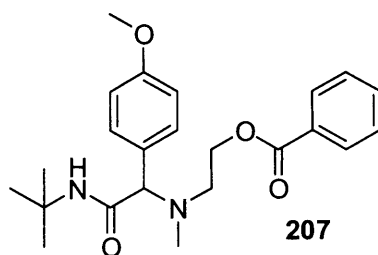
¹³C NMR (CDCl₃) δ 9.0, 14.0, 22.7, 27.3, 27.5, 28.7, 29.2, 30.0, 38.4, 51.0, 53.3, 62.0, 68.9, 172.3, 174.3.

HRMS - (FAB (pos)) - calculated for C₁₈H₃₇N₂O₃: 329.28040, found 329.28191.

LRMS - (FAB (pos)) 228 (100), 329 (24, M+H), 229 (15), 170 (7), 327 (7), 226 (6).

IR (thin film) ν max- 3330 br (NH), 2951 (alkyl), 2930 (alkyl), 2858 (alkyl), 1746 (C=O), 1662 (C=O), 1510 (NH), 1456 cm⁻¹.

2-[(*tert*-Butylcarbamoyl-(4-methoxy-phenyl)-methyl)methyl-amino]-ethyl benzoate **207**.



Method A

2-(4-Methoxy-phenyl)-3-methyl-oxazolidine **181** (387 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μ l, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of nitrogen for 18 h. Excess solvent was removed under reduced pressure and the crude residue was purified by column chromatography (4:1 hexanes:EtOAc) to give 2-*{[tert-butylcarbamoyl-(4-methoxy-phenyl)-methyl]methyl-amino}*-ethyl benzoate **207** (542 mg, 68 %) as a colourless oil. R.f = 0.40 (2:1 hexanes:EtOAc).

Method B

2-(Methylamino)-ethanol (161 μ l, 2 mmol), *p*-anisaldehyde (243 μ l, 2 mmol), benzoic acid (244 mg, 2 mmol) and *p*TsOH (8 mg, 0.04 mmol) were added to anhydrous IPA (2 ml), *tert*-Butyl isocyanide (166 mg / 226 μ l, 2 mmol) was then added and the mixture heated at reflux for 17h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1 hexanes:EtOAc) to give 2-*{[tert-butylcarbamoyl-(4-methoxy-phenyl)-methyl]methyl-amino}*-ethyl benzoate **207** (527 mg, 66 %) as a colourless oil.

¹H NMR (CDCl₃) δ 1.27 (9H, s, *t*-Bu), 2.33 (3H, s, N-CH₃), 2.67-2.85 (2H, m, N-CH₂), 4.02 (3H, s, O-CH₃), 4.06 (1H, s, CH), 4.32-4.62 (2H, m, O-CH₂), 6.78 (2H, d, *J* = 6.8 Hz, *m*-PhOMe), 7.04 (1H, bs, NH), 7.17 (2H, d, *J* = 6.8 Hz, *o*-PhOMe), 7.32-7.53 (3H, m, Ar), 8.00 (2H, d, *J* = 8.5 Hz, Ar).

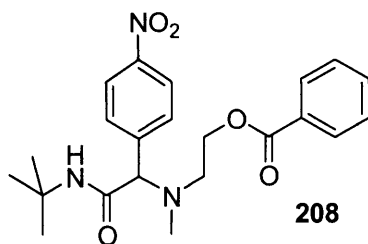
¹³C NMR (CDCl₃) δ 28.5, 40.4, 50.6, 53.4, 62.3, 75.1, 113.8, 128.1, 128.4, 129.6, 130.1, 130.2, 132.5, 133.1, 159.4, 166.4, 170.9.

HRMS - (FAB (pos)) - calculated for C₂₃H₃₁N₂O₄: 399.22837, found 399.22720.

LRMS - (FAB (pos)) 399 (100, M+H), 298 (68), 400 (27), 220 (23), 192 (14), 299 (13).

IR (thin film) ν max- 3390 br (NH), 2980 (alkyl), 2970 (alkyl), 2930 (alkyl), 2885 (alkyl), 1716 (C=O), 1678 (C=O), 1510 (NH), 1452 cm^{-1} .

2- $\{[tert\text{-}Butylcarbamoyl\text{-}4\text{-}nitro\text{-}phenyl)\text{-}methyl]\text{-}methyl\text{-}amino\}\text{-}ethyl\text{ benzoate}$ **208**.



Method A

3-Methyl-2-(4-nitro-phenyl)-oxazolidine **182** (416 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μl , 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of nitrogen for 18 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (3:1 hexanes:EtOAc) to give 2- $\{[tert\text{-}butylcarbamoyl\text{-}4\text{-}nitro\text{-}phenyl)\text{-}methyl]\text{-}methyl\text{-}amino\}\text{-}ethyl\text{ benzoate}$ **208** (389 mg, 47 %) as an orange oil. R.f. = 0.29 (2:1 hexanes:EtOAc).

Method B

2-(Methylamino)-ethanol (161 μl , 2 mmol), *p*-nitrobenzaldehyde (302 mg, 2 mmol), benzoic acid (244 mg, 2 mmol) and *p*TsOH (8 mg, 0.04 mmol) were added to anhydrous IPA (2 ml), *tert*-Butyl isocyanide (166 mg / 226 μl , 2 mmol) was then added and the mixture heated at reflux for 17h. Excess solvent was removed under reduced pressure and the residue was purified by column chromatography (4:1 hexanes:EtOAc) to give 2- $\{[tert\text{-}butylcarbamoyl\text{-}4\text{-}nitro\text{-}phenyl)\text{-}methyl]\text{-}methyl\text{-}amino\}\text{-}ethyl\text{ benzoate}$ **208** (247 mg, 30 %) as an orange oil.

¹H NMR (CDCl₃) δ 1.26 (9H, s, *t*-Bu), 2.30 (3H, s, N-CH₃), 2.67-2.88 (2H, t, J= 5.6 Hz N-CH₂), 4.18 (1H, s, CH), 4.41(2H, m, O-CH₂), 6.98 (1H, bs, NH), 7.39-7.47 (4H, m, Ar), 7.52-7.57 (1H, m, Ar), 8.01 (2H, d, J= 8.6 Hz, Ar), 8.12 (2H, d, J= 8.6 Hz, Ar).

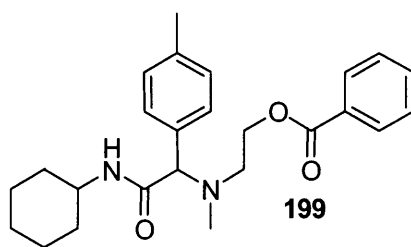
¹³C NMR (CDCl₃) δ 28.5, 40.0, 51.0, 53.8, 61.9, 74.7, 123.5, 128.5, 129.6, 129.9, 130.2, 133.3, 143.0, 147.5, 166.4, 169.1.

HRMS - (FAB (pos)) - calculated for C₂₂H₂₇N₃NaO₅: 437.19099, found 437.19266.

LRMS - (FAB (pos)) 176 (100), 313 (80), 360 (47), 174 (46), 436 (34), 330 (32).

IR (thin film) ν max- 3300 br (NH), 3057 (aryl), 2991 (alkyl), 2894 (alkyl), 2807 (N-CH₃), 1716 (C=O ester), 1682 (C=O amide), 1521 (NH), 1452 cm⁻¹.

2-[(Cyclohexylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]-ethyl benzoate **199**.



3-Methyl-2-*p*-tolyl-oxazolidine **179** (355 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then cyclohexyl isocyanide (218 mg / 248 μl, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of nitrogen for 18 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1 hexanes:EtOAc) to give 2-[(cyclohexylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]-ethyl benzoate **199** (580 mg, 71 %) as a pale yellow oil. R.f. = 0.14 (2:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 0.95-1.81 (10H, complex m, Cy), 2.27 (3H, s, tolyl-CH₃), 2.29 (3H, s, N-CH₃), 2.67-2.81 (2H, m, N-CH₂), 4.00 (1H, s, CH), 4.30-4.43 (1H, m,

CH_AH_B-O), 4.30-4.43 (1H, m, CH_AH_B-O), 6.93 (1H, bs, NH), 7.03-7.54 (7H, m, Ar), 8.00-8.05 (2H, m, Ar).

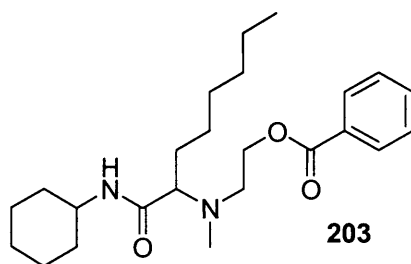
¹³C NMR (CDCl₃) δ 21.1, 28.6, 40.5, 50.7, 53.5, 75.6, 128.4, 129.0, 129.2, 129.7, 130.1, 132.9, 133.1, 137.8, 166.5, 170.8.

HRMS - (FAB (pos)) - calculated for C₂₅H₃₂N₂NaO₃: 431.23105, found 431.23051.

LRMS - (FAB (pos)) 431 (100, M+Na), 432 (35), 282 (23), 360 (14), 149 (10), 201 (8).

IR (thin film) ν max- 3310 (NH), 2922 (alkyl), 2852 (alkyl), 1726 (C=O ester), 1651 (C=O amide), 1562 (NH), 1460 cm⁻¹.

2-[(1-Cyclohexylcarbamoyl-heptyl)-methyl-amino]-ethyl benzoate **203**.



Method A

2-Hexyl-3-methyl-oxazolidine **180** (343 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then cyclohexyl isocyanide (218 mg / 248 μl, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of nitrogen for 18 h. Excess solvent was removed under reduced pressure and the residue was purified by column chromatography (4:1 hexanes:EtOAc) to give 2-[(1-cyclohexylcarbamoyl-heptyl)-methyl-amino]-ethyl benzoate **203** (383 mg, 48 %) as a colourless oil. R.f. = 0.26 (2:1 hexanes:EtOAc).

Method B

2-(Methylamino)-ethanol (161 μ l, 2 mmol), 1-heptanal (279 μ l, 2 mmol), benzoic acid (244 mg, 2 mmol) and *p*TsOH (8 mg, 0.04 mmol) were added to anhydrous IPA (2 ml), cyclohexyl isocyanide (248 μ l, 2 mmol) was then added and the mixture refluxed for 17h. Excess solvent was removed under reduced pressure and the residue was purified by column chromatography (4:1 hexanes:EtOAc) to give 2-[(1-cyclohexylcarbamoyl-heptyl)-methyl-amino]-ethyl benzoate **203** (346 mg, 43 %) as a colourless oil.

^1H NMR (CDCl_3) δ 0.86 (3H, t, J = 7.0 Hz, CH_3), 0.88-1.05 (3H, m, alkyl), 1.20 (9H, bs, alkyl), 1.32-1.80 (8H, m, alkyl), 2.27 (3H, s, N- CH_3), 2.83-2.97 (2H, m, N- CH_2), 3.53-3.61 (1H, m, CH), 4.28-4.42 (2H, m, $\text{CH}_2\text{-O}$), 6.82 (1H, d, J = 8.5 Hz, NH), 7.36-7.41 (2H, m, Ar), 7.47-7.51 (1H, m, Ar), 7.96-8.01 (2H, m, Ar).

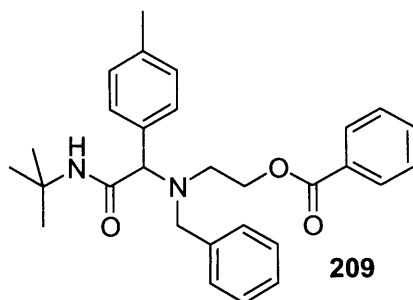
^{13}C NMR (CDCl_3) δ 14.0, 22.6, 24.8, 25.4, 27.3, 27.5, 29.5, 31.7, 32.8, 33.1, 38.4, 47.5, 53.8, 62.6, 68.5, 128.4, 129.6, 130.1, 133.1, 166.5, 171.9.

HRMS - (FAB (pos)) - calculated for $\text{C}_{24}\text{H}_{39}\text{N}_2\text{O}_3$: 403.29605, found 403.29553.

LRMS - (FAB (pos)) 276 (100), 403 (81, $\text{M}+\text{H}$), 402 (23), 267 (20), 401 (15), 154 (12).

IR (thin film) ν max- 3315 br (NH), 2930 (alkyl), 2955 (alkyl) 1717 ($\text{C}=\text{O}$ ester), 1647 ($\text{C}=\text{O}$ amide), 1510 (NH), 1452 cm^{-1} .

2-[Benzyl-(tert-butylcarbamoyl-*p*-tolyl-methyl)-amino]ethyl benzoate **209**.



Benzyl-2-p-tolyl-oxazolidine **183** (507 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μ l, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of nitrogen for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by flash chromatography (6:1 hexanes:EtOAc) to yield 2-[*benzyl-(tert-butylcarbamoyl-p-tolyl-methyl)-amino*]ethyl benzoate **209** as a yellow oil (404 mg, 44 %). R.f. = 0.58 (2:1 hexanes:EtOAc).

^1H NMR (CDCl_3) δ 1.26 (9H, s, *t*-Bu), 2.34 (3H, s, tolyl- CH_3), 2.79-2.98 (2H, m, N- CH_2), 3.53-3.58 (1H, d, $J = 4.7$ Hz, Ar- $\text{CH}_\text{A}\text{H}_\text{B}$), 3.87-3.92 (1H, d, $J = 4.7$ Hz, Ar- $\text{CH}_\text{A}\text{H}_\text{B}$), 4.20-4.49 (2H, m, $\text{CH}_2\text{-O}$), 4.39 (1H, s, CH), 6.96 (1H, bs, NH), 7.13-7.98 (14H, m, Ar).

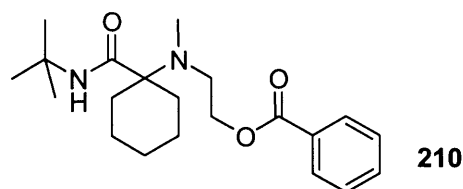
^{13}C NMR (CDCl_3) δ 21.2, 28.7, 49.2, 50.9, 56.3, 62.6, 70.2, 127.4, 128.4, 128.5, 129.0, 129.7, 129.9, 130.2, 132.1, 133.1, 137.6, 138.8, 166.5, 170.8.

HRMS - (FAB (pos)) - calculated for $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_3$: 459.26475, found 459.26337.

LRMS - (FAB (pos)) 358 (100), 459 (99, $\text{M}+\text{H}$), 359 (42), 359 (37), 178 (18), 457 (13).

IR (thin film) ν max- 3342 br (NH) 2924 (alkyl), 1717 ($\text{C}=\text{O}$), 1678 ($\text{C}=\text{O}$), 1510 (NH) cm^{-1} .

2-[(1-*tert*-Butylcarbamoyl-cyclohexyl)-methyl-amino]-ethyl benzoate **210**.



4-Methyl-1-oxa-4-aza-spiro[4.5]decane **184** (310 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μ l, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an

atmosphere of nitrogen for 24 h. Excess solvent was removed under reduced pressure and the residue was purified by flash chromatography (4:1 hexanes:EtOAc) to yield *2-[(1-tert-Butylcarbamoyl-cyclohexyl)-methyl-amino]-ethyl benzoate 210* as a colourless oil (455 mg, 63 %). R.f. = 0.63 (2:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 1.19 (9H, s, *t*-Bu), 1.30-1.37 (2H, m, CH₂) 1.51-1.91 (8H, m, CH₂), 2.21 (3H, s, N-CH₃), 2.68 (2H, t, J= 6.0 Hz, N-CH₂,), 4.28 (2H, t, J= 6.1 Hz O-CH₂), 6.22 (1H, bs, NH), 7.04-7.41 (3H, m, Ar), 7.92 (2H, d, J= 9.4 Hz, Ar).

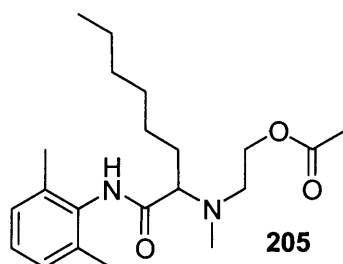
¹³C NMR (CDCl₃) δ 22.9, 25.9, 28.6, 30.2, 36.0, 49.8, 50.1, 63.7, 66.4, 128.3, 129.9, 130.1, 132.9, 166.3, 174.4.

HRMS - (FAB (pos)) - calculated for C₂₁H₃₃N₂O₃: 361.24910, found 361.24790.

LRMS - (FAB (pos)) 260 (100), 361 (91, M+H), 154 (55), 362 (22), 155 (20), 261 (18).

IR (thin film) ν max- 3380 br (NH), 2973 (alkyl), 2944 (alkyl), 2870 (alkyl), 1710 (C=O), 1680 (C=O), 1505 (NH), 1465 cm⁻¹.

3-{[1-(2,6-Dimethyl-phenylcarbamoyl)-heptyl]-methyl-amino}ethyl propionate 205.



Hexyl-3-methyl-oxazolidine **180** (262 mg, 2 mmol), propionic acid (149 µl, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 µl, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of nitrogen for 18 h. Excess solvent was removed under reduced pressure and the crude product was purified by flash chromatography (5:1 hexanes:EtOAc) to yield *3-{[1-*

(2,6-dimethyl-phenylcarbamoyl)-heptyl]-methyl-amino}-ethyl propionate **205** as a colourless oil (320 mg, 42 %). R.f. =0.40 (2:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 0.88 (3H, t, J= 6.6 Hz, CH₃), 1.02 (3H, t, J= 7.5 Hz, COCH₂CH₃), 1.25-1.58 (10H, m, CH₂), 1.63-1.78 (1H, m, CH₂), 1.88-2.00 (1H, m, CH₂), 2.21 (6H, s, Ar-CH₃), 2.45 (3H, s, N-CH₃), 2.91 (2H, m, N-CH₂), 3.25 (1H, t, J= 6.5 Hz, CH), 4.22 (2H, t, J= 5.5 Hz, CH₂-O), 7.01 (3H, s, Ar), 8.65 (1H, bs, NH).

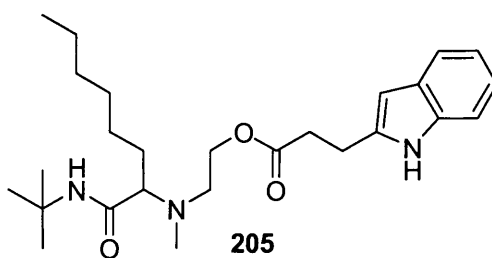
¹³C NMR (CDCl₃) δ 8.9, 14.1, 18.7, 22.6, 27.33, 27.38, 29.6, 31.7, 38.8, 54.0, 62.1, 68.6, 126.8, 128.8, 134.1, 134.9, 171.4, 174.4.

HRMS - (FAB (pos)) - calculated for C₂₂H₃₆N₂NaO₃: 399.26235, found 399.26169.

LRMS - (FAB (pos)) 399 (100, M+Na), 228 (40), 400 (24), 229 (5), 377 (4).

IR (thin film) ν max- 3300 br (NH), 3020 (aryl), 2955 (alkyl), 2928 (alkyl), 2856 (alkyl), 1738 (C=O ester), 1674 (C=O amide), 1468 cm⁻¹.

3-(1H-Indol-3-yl)-2-[(1-tert-butylcarbamoyl-heptyl)-methyl-amino-ethyl propionate **204**.



Hexyl-3-methyl-oxazolidine **180** (343 mg, 2 mmol), 3-indole propionic acid (378 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μl, 2 mmol) were added to anhydrous MeCN (5 ml) and heated to reflux under an atmosphere of nitrogen for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by flash chromatography (6:1 hexanes:EtOAc) to give 3-(1H-indol-3-yl)-2-[(1-tert-butylcarbamoyl-heptyl)-methyl-amino-ethyl propionate **204** (388 mg, 44 %) as a colourless oil. R.f.= 0.12 (2:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 0.89 (3H, t, J= 6.8 Hz, CH₃), 1.20-1.32 (8H, m, CH₂), 1.37 (9H, s, *t*-Bu), 1.50-1.64 (1H, m, CH_AH_B-alkyl), 1.68-1.82 (1H, m, CH_AH_B-alkyl), 2.26 (3H, s, N-CH₃), 2.62-2.72 (2H, m, N-CH₂), 2.75 (2H, t, J= 7.5 Hz, CO-CH₂), 2.87 (1H, t, J= 5.4 Hz, CH), 3.13 (2H, t, J= 7.5 Hz, C=C-CH₂), 4.17 (2H, t, J= 5.6 Hz, O-CH₂), 6.92 (1H, s, NH), 6.97 (1H, s, C=CH), 7.11 (1H, t, J= 7.2 Hz, Ar), 7.18 (1H, t, J= 7.1 Hz, Ar), 7.34 (1H, d, J= 7.8 Hz, Ar), 7.69 (1H, d, J= 7.7 Hz, Ar), 8.84 (1H, bs, NH indole).

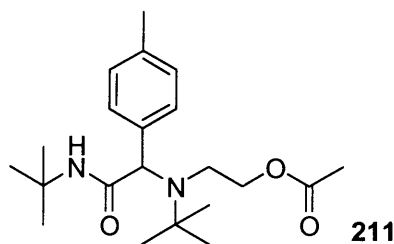
¹³C NMR (CDCl₃) δ 14.1, 20.8, 22.7, 27.3, 27.6, 28.8, 29.6, 31.7, 35.1, 38.5, 50.5, 53.4, 62.3, 69.1, 111.4, 114.3, 118.5, 119.1, 121.76, 121.82, 127.1, 136.5, 172.6, 173.5.

HRMS - (FAB (pos)) - calculated for C₂₅H₄₀N₃O₃: 443.31479, found 443.31388.

LRMS - (FAB (pos)) 343 (100), 444 (65), 344 (23), 445 (18), 154 (14), 172 (12).

IR (thin film) ν max- 3300 br (NH), 3387 br (NH), 3020 (aryl), 2959 (alkyl), 2930 (alkyl), 2858 (alkyl), 1732 (C=O), 1666 (C=O), 1514 (NH), 1456 cm⁻¹.

2-(*tert*-Butyl(2-(*tert*-butylamino)-2-oxo-1-*p*-tolylethyl)amino)ethyl acetate **211**.



3-*tert*-Butyl-2-*p*-tolyl-oxazolidine **185** (438 mg, 2 mmol), acetic acid (120 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μl, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of nitrogen for 48 h. Excess solvent was removed under reduced pressure and the crude product was purified by flash chromatography (4:1 hexanes:EtOAc) to

give 2-[*tert*-butyl-(*tert*-butylcarbamoyl-*p*-tolyl-methyl)-amino]ethyl-acetate **211** (145 mg, 20 %) as a colourless oil. R.f. = 0.40 (2:1 hexanes:EtOAc). (Crystallised by slow evaporation from CHCl₃ (needles), (m.p. = 90-91 °C).

¹H NMR (CDCl₃) δ 1.16 (9H, s, *t*-Bu), 1.41 (9H, s, *t*-Bu), 2.00 (3H, s, CO₂CH₃), 2.28 (3H, s, tolyl-CH₃), 2.30-2.41 (1H, m, N-CH_AH_B), 2.81-2.92 (1H, m, N-CH_AH_B), 3.58-3.67 (1H, m, O-CH_AH_B), 3.78-3.87 (1H, m, O-CH_AH_B), 4.55 (1H, s, CH), 7.01 (2H, d, J= 8.1 Hz, Ar), 7.08 (2H, d, J= 8.1 Hz, Ar), 7.83 (1H, bs, NH).

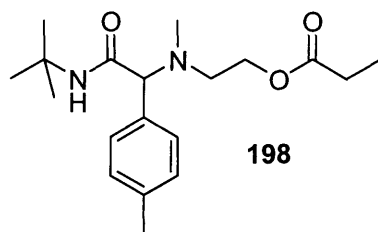
¹³C NMR (CDCl₃) δ 21.1, 27.9, 28.7, 42.8, 50.6, 56.7, 129.5, 130.2, 134.4, 137.3, 170.7, 174.0.

HRMS - (CI (pos) methane) - calculated for C₂₂H₃₇N₂O₃: 363.26475, found 363.26552.

LRMS - (CI (pos) methane) 262 (100), 206 (71), 307 (32), 119 (22), 263 (17), 176 (15).

IR (KBr Disc) ν max- 3314 br (NH), 2968 (alkyl), 2924 (alkyl), 1738 (C=O ester), 1670 (C=O amide), 1506 (NH), 1456 cm⁻¹.

2-[(*tert*-Butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]-ethyl propionate **198**.



3-Methyl-2-*p*-tolyl-oxazolidine **179** (355 mg, 2 mmol), propionic acid (150 μl, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and *tert*-butyl isocyanide (166 mg, 226 μl, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of argon for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1

isohexane:EtOAc) to yield 2-[(*tert*-butylcarbamoyl-*p*-tolyl-methyl)-methylamino] ethyl propionate **198** as a colourless oil (428 mg, 64 %). R.f . = 0.26 (2:1 isohexane:EtOAc).

¹H NMR (CDCl₃, 400 MHz) δ 1.08 (3H, t, J= 7.7 Hz, CH₂-CH₃), 1.28 (9H, s, *t*-Bu), 2.14 (3H, s, tolyl-CH₃), 2.25 (3H, s, N-CH₃), 2.27 (2H, q, J= 7.7 Hz, CH₂-CH₃), 2.54 (2H, t, J= 5.8 Hz, N-CH₂), 3.76 (1H, s, CH), 4.10 (2H, t, J= 5.8 Hz, O-CH₂), 6.23 (1H, bs, NH), 7.03-7.10 (4H, m, Ar).

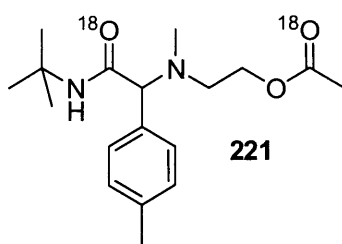
¹³C NMR (CDCl₃, 100 MHz) δ 9.5, 21.5, 28.0, 40.7, 51.0, 53.9, 62.3, 76.3, 129.2, 129.5, 133.6, 138.1, 171.2, 174.7.

HRMS - (FAB (pos)) - calculated for C₁₉H₃₁N₂O₃: 335.23346, found 335.23240.

LRMS - (FAB (pos)) 154 (100), 155 (83), 307 (78), 335 (44, M+H), 289 (30), 308 (22).

IR (thin film) ν max- 3404 br (NH), 3054 (aryl), 2970 (alkyl), 2926 (alkyl), 2826 (N-CH₃), 1737 (C=O ester), 1664 (C=O), 1513 (NH), 1456 cm⁻¹.

2-[(*tert*-Butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino] ethyl acetate ¹⁸O₂ **221**.



3-Methyl-2-*p*-tolyl-oxazolidine **179** (138 mg, 0.78 mmol), acetic acid-¹⁸O₂ (95 atom % ¹⁸O) (50 mg, 0.78 mmol), *p*TsOH (15 mg, 0.078mmol) and *tert*-butyl isocyanide (88 μl, 0.78 mmol) were added to anhydrous MeCN (2 ml) and heated at reflux under an atmosphere of argon for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1 isohexane:EtOAc) to yield 2-[(*tert*-butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]

¹⁸O₂ ethyl acetate **221** as a colourless oil (120 mg, 47 %). R.f. = 0.37 (2:1 isohexane:EtOAc).

¹H NMR (CDCl₃, 400 MHz) δ 1.28 (9H, s, *t*-Bu), 2.06 (3H, s, COCH₃), 2.15 (3H, s, tolyl-CH₃), 2.24 (3H, s, N-CH₃), 2.57-2.62 (2H, m, N-CH₂), 3.83 (1H, s, CH), 4.10 (2H, dt, J= 5.7, 1.2 Hz, O-CH₂), 6.99 (1H, bs, NH), 7.10 (2H, d, J= 8.0 Hz, Ar), 7.14 (2H, d, J= 8.0 Hz, Ar).

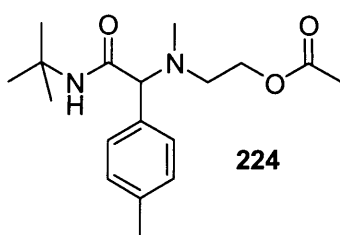
¹³C NMR (CDCl₃, 100 MHz) δ 20.9, 21.0, 28.5, 40.0, 50.6, 53.3, 61.6, 75.5, 128.6, 128.8, 129.0, 129.2, 137.7, 137.9, 170.3 (br), 170.7.

HRMS - (FAB (pos)) - calculated for C₁₈H₂₉N₂O¹⁸O₂: 325.22630, found 325.22528

LRMS - (FAB (pos)) 154 (100), 155 (65), 307 (55), 325 (45, M+H), 289 (24), 156 (17).

IR (thin film) ν max- 3360 br (NH), 2966 (alkyl), 2920 (alkyl), 2884 (alkyl), 1708 (C=O ester), 1643 (C=O amide), 1512 (NH), 1456 cm⁻¹.

2-[(*tert*-Butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino] ethyl acetate **224**.



3-Methyl-2-*p*-tolyl-oxazolidine **180** (355 mg, 2 mmol), acetic acid (116 μl, 2 mmol), *p*TsOH (8 mg, 0.04 mmol) and then *tert*-butyl isocyanide (226 μl, 2 mmol) were added to anhydrous IPA (2 ml) and heated at reflux under an atmosphere of argon for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1 isohexane:EtOAc) to yield 2-[(*tert*-butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino] ethyl acetate **224** as a colourless oil (346 mg, 54%). R.f. = 0.40 (2:1 isohexane:EtOAc).

^1H NMR (CDCl_3 , 400 MHz) δ 1.28 (9H, s, t-Bu), 2.09 (3H, s, COCH_3), 2.16 (3H, s, tolyl- CH_3), 2.23 (3H, s, N- CH_3), 2.54 (2H, t, $J = 5.6$ Hz, N- CH_2), 3.76 (1H, s, CH), 4.09 (2H, dt, $J = 5.6, 1.2$ Hz, O- $\text{CH}_\text{A}\text{H}_\text{B}$), 6.95 (1H, bs, NH), 7.11 (2H, d, $J = 8.0$ Hz, Ar), 7.23 (2H, d, $J = 8.0$ Hz, Ar).

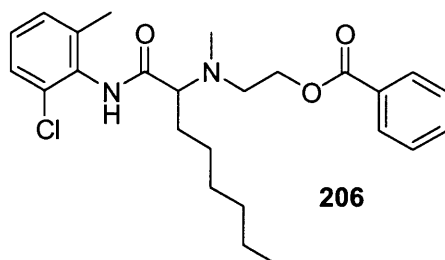
^{13}C NMR (CDCl_3 , 100 MHz) δ 21.1, 21.2, 28.7, 40.2, 51.5, 61.9, 75.5, 127.5, 128.8, 129.1, 133.0, 138.8, 167.4, 169.2.

HRMS - (EI) - calculated for $\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}_3$: 321.2173, found 321.2155.

LRMS - (EI) 176 (100), 321 (78, M+H), 220 (54), 343 (17, M+Na), 177 (12), 221 (8).

IR (thin film) ν max- 3330 br (NH), 2987 (alkyl), 2943 (alkyl), 2872 (alkyl), 2875 (alkyl), 1732 ($\text{C}=\text{O}$ ester), 1667 ($\text{C}=\text{O}$ amide), 1515 (NH), 1455 cm^{-1}

2-{[1-(2-Chloro-6-methyl-phenylcarbamoyl)-heptyl]-methyl-amino}-ethyl benzoate **206**.



2-Hexyl-3-methyl-oxazolidine **180** (343 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then 2-chloro-6-methyl isocyanide (303 mg, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of argon for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1 isohexane:EtOAc) to yield 2-{[1-(2-chloro-6-methyl-phenylcarbamoyl)-heptyl]-methyl-amino}-ethyl benzoate **206** as a colourless oil (258 mg, 29 %). R.f. = 0.18 (2:1 isohexane:EtOAc).

¹H NMR (CDCl₃, 400 MHz) δ 0.77 (3H, t, J = 6.9 Hz, CH₂CH₃), 1.16-1.28 (6H, m, CH₂), 1.32-1.47 (2H, m, CH₂), 1.65-1.75 (1H, CH₂), 1.87-1.94 (1H, m, CH₂), 2.10 (3H, s, N-CH₃), 2.55 (3H, s, Ar-CH₃), 3.13 (2H, t, J = 5.6 Hz, O-CH₂), 3.53 (1H, dd, J = 7.1 Hz, 6.0 Hz, CH), 4.45-4.90 (2H, t, J = 5.6 Hz, O-CH₂), 7.05-7.32 (2H, m, Ar), 7.44-7.49 (2H, m, Ar), 7.57-7.61 (1H, m, Ar), 7.95-8.00 (1H, m, Ar), 8.11 (2H, m, Ar), 8.70 (1H, bs, NH).

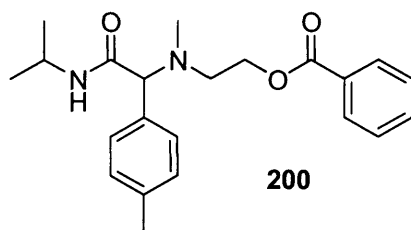
¹³C NMR (CDCl₃, 100 MHz) δ 13.9, 18.9, 22.5, 27.2, 27.5, 29.3, 31.5, 38.4, 53.6, 62.0, 68.3, 127.0, 127.5, 128.17, 128.23, 129.0, 129.4, 130.0, 132.9, 133.2, 137.6, 166.4, 171.3.

HRMS - (FAB (pos)) - calculated for C₂₅H₃₄ClN₂O₃: 445.2258, found 445.2266.

LRMS - (FAB (pos)) 445 (100, M+H (³⁵Cl)), 447 (33, M+H (³⁷Cl)), 446 (23), 448 (25), 444 (2), 432 (1).

IR (thin film) ν max- 3280 br (NH), 2961 (alkyl), 2919 (alkyl), 2874 (alkyl), 1719 (C=O ester), 1676 (C=O amide), 1467 cm⁻¹.

2-[(Isopropylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]-ethyl benzoate **200**.



3-Methyl-2-*p*-tolyl-oxazolidine **179** (355 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol) and then isopropyl isocyanide (*warning – cyanide like effects*)* (189 mg, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of argon for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1

isohexane:EtOAc) to afford the title compound **200** as a colourless oil (535 mg, 73 %). R.f. = 0.21 (2:1 isohexane:EtOAc).

¹H NMR (CDCl₃, 400 MHz) δ 1.00 (3H, d, J= 6.6 Hz, CH-CH₃), 1.07 (3H, d, J= 6.6 Hz, CH-CH₃), 2.28 (3H, s, N-Me or Ar-CH₃), 2.29 (3H, s, N-Me or Ar-CH₃), 2.63-2.70 (1H, m, N-CH_AH_B), 2.72-2.80 (1H, m, N-CH_AH_B), 3.96 (1H, s, C=OCH), 3.99-4.05 (1H, m, CH-(CH₃)₂), 4.35-4.41 (1H, m O-CH_AH_B), 4.46-4.52 (1H, m, O-CH_AH_B), 6.91 (1H, d, J= 8.3 Hz, NH), 7.10 (2H, d, J= 7.6 Hz, Ar), 7.16-7.20 (2H, m, Ar), 7.39-7.48 (2H, m, Ar), 7.56-7.62 (1H, m, Ar), 8.04-8.09 (2H, m, Ar).

¹³C NMR (CDCl₃, 100 MHz) δ 21.0, 22.4, 40.4, 40.7, 53.4, 62.2, 62.3, 75.1, 128.3, 128.8, 129.1, 129.5, 130.0, 132.9, 133.0, 137.7, 166.4, 170.5.

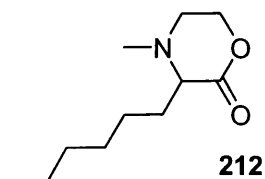
HRMS - (FAB (pos)) - calculated for C₂₂H₂₉N₂O₃: 369.2178, found 369.2177.

LRMS - (FAB (pos)) 369 (100, M+H), 370 (20), 371 (4), 317 (1), 247 (1), 190 (1).

IR (thin film) ν max- 3420 br (NH), 2985 (alkyl), 2968 (alkyl), 1739 (C=O ester), 1651 (C=O amide), 1506 (NH), 1452 cm⁻¹.

*= Care, this material can produce a cyanide like effect! Always have a cyanide first-aid kit present when using this material. The onset of symptoms is generally delayed pending conversion to cyanide.

3-Hexyl-4-methyl-morpholin-2-one **212**.



2-Hexyl-3-methyl-oxazolidine **180** (343 mg, 2 mmol), *p*TsOH (419 mg, 2.2 mmol) and then *tert*-butyl isocyanide (226 μ l, 2 mmol) were added to reagent grade DMSO (5 ml) and heated to 75°C under an atmosphere of nitrogen for 24 h. The reaction was cooled to r.t. and sat. NaHCO₃ (aq) (5 ml) and EtOAc (5 ml) were added. The organic layer was separated and the aqueous layer was further extracted with EtOAc (2 x 5 ml). The combined organic layers were then washed with brine (5 ml), dried

(MgSO₄), filtered and evaporated under reduced pressure. Purification by column chromatography (3:1 hexanes:EtOAc) gave *3-hexyl-4-methyl-morpholin-2-one* **212** as a colourless oil (277 mg, 69 %). R.f. = 0.25 (2:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 0.83 (3H, t, J= 6.8 Hz, CH₂CH₃), 1.23-1.32 (7H, m, alkyl), 1.45-1.54 (1H, m, alkyl), 1.70-1.78 (1H, m, alkyl), 1.88-2.02 (1H, m, alkyl), 2.30 (3H, s, N-CH₃), 2.60 (1H, ddd, J= 12.8, 11.1, 3.3 Hz, N-CH_ACH_B), 2.84 (1H, dt, J= 9.8, 2.7 Hz, N-CH_ACH_B), 2.99 (1H, t, J= 4.9 Hz, CH), 4.23-4.27 (1H, ddd, J= 10.8, 3.2, 2.3 Hz, O-CH_ACH_B), 4.38 (1H, td, J= 10.9, 3.1 Hz, O-CH_ACH_B).

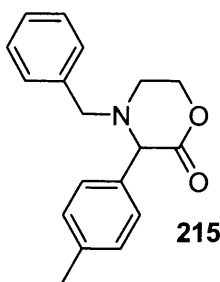
¹³C NMR (CDCl₃) δ 14.0, 22.6, 24.7, 29.3, 30.1, 31.7, 43.1, 51.1, 67.0, 67.7, 170.5.

HRMS - (CI (pos) methane) - calculated for C₁₁H₂₂NO₂: 200.16505, found 200.16432

LRMS - (CI (pos) methane) 216 (100, M+CH₄), 160 (49), 200 (26), 131 (17), 217 (15), 214 (14).

IR (thin film) ν max- 2963 (alkyl), 2931 (alkyl), 2874 (alkyl), 2867 (alkyl), 1738 (C=O ester), 1552 1459 cm⁻¹.

4-(4-Methyl-benzyl)-3-p-tolyl-morpholin-2-one **215**.



Benzyl-2-p-tolyl-oxazolidine **183** (130 mg, 0.5 mmol), *p*TsOH (106 mg, 0.55 mmol) and then *tert*-butyl isocyanide (62 μl, 0.5 mmol) were added to reagent grade DMSO (1.25 ml) and heated to 80°C under an atmosphere of nitrogen for 24 h. The reaction was cooled to r.t. and sat. NaHCO₃ (aq) (2 ml) and EtOAc (2 ml) were added. The upper organic layer was separated and the aqueous layer was further extracted with

EtOAc (2 x 2 ml). The combined organic layers were washed with brine (2 ml), dried (MgSO₄), filtered and evaporated under reduced pressure. Purification by column chromatography (3:1 hexanes:EtOAc) gave *4-(4-methyl-benzyl)-3-p-tolyl-morpholin-2-one* **215** as a colourless oil (87 mg, 62 %). R.f. = 0.45 (2:1 hexanes:EtOAc).

¹H NMR (CDCl₃, 400MHz) δ 2.27 (3H, s, Ar-CH₃), 2.55 (1H, ddd, J= 12.7, 11.0, 3.2 Hz, N-CH_ACH_B), 2.90 (1H, dt, J= 12.7, 2.7 Hz, N-CH_ACH_B), 3.08 (1H, d, J=13.1 Hz, Ar-CH_ACH_B), 3.71 (1H, d, J= 13.4 Hz, Ar-CH_ACH_B), 4.14 (1H, s, CH), 4.27 (1H, ddd, J= 10.8, 3.2, 2.4 Hz, O-CH_ACH_B), 4.46 (1H, td, 11.0, 3.2 Hz, O-CH_ACH_B). 7.11 (1H, m, Ar), 7.14 (1H, m, Ar), 7.16 (1H, m, Ar), 7.17 (2H, d, J= 1.2 Hz, Ar), 7.21 (1H, d, J= 2.8 Hz), 7.23 (1H, t, J=1.6 Hz, Ar), 7.36 (1H, t, J= 1.6 Hz, Ar), 7.38 (1H, t, J= 1.6 Hz, Ar).

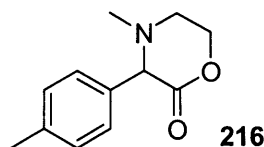
¹³C NMR (CDCl₃, 100MHz) δ 21.5, 47.1, 59.2, 69.0, 70.7, 127.9, 128.7, 129.20, 129.23, 129.9, 134.9, 137.5, 138.6, 169.3.

HRMS - (ES (pos)) - calculated for C₁₈H₂₀NO₂: 282.14940, found 282.14894.

LRMS -(ES (pos)) 282 (100, M+H), 177 (55), 233 (38), 304 (23, M+Na), 283 (17), 276 (13).

IR (thin film) ν max- 3018 (aryl), 2973 (alkyl), 1742 (C=O ester), 1512, 1452 cm⁻¹.

4-Methyl-3-*p*-tolylmorpholin-2-one **216**.



3-Methyl-2-*p*-tolyl-oxazolidine **179** (355 mg, 2 mmol), *p*TsOH (419 mg, 2.2 mmol) and then *tert*-butyl isocyanide (226 μ l, 2 mmol) were added to DMSO (5 ml) and heated to 75°C under an atmosphere of nitrogen for 24 h. The reaction was cooled to r.t. and sat. NaHCO₃ (aq) (5 ml) and EtOAc (5 ml) were added. The upper organic

layer was separated and the aqueous layer was further extracted with EtOAc (2 x 5 ml). The combined organic layers were then washed with brine (5 ml), dried (MgSO_4), filtered and evaporated under reduced pressure. Purification by column chromatography (2:1 hexanes:EtOAc) gave 4-methyl-3-p-tolylmorpholin-2-one **216** as a colourless oil (226 mg, 55 %). R.f. = 0.10 (2:1 hexanes:EtOAc).

^1H NMR (CDCl_3 , 400 MHz) δ 2.19 (3H, s, tolyl- CH_3 or N- CH_3), 2.32 (3H, s, tolyl- CH_3 or N- CH_3), 2.79-2.84 (1H, m, N- $\text{CH}_\text{A}\text{CH}_\text{B}$), 3.00 (1H, ddd, J = 12.7, 3.0, 1.9 Hz, N- $\text{CH}_\text{A}\text{CH}_\text{B}$), 3.87 (1H, s, CH), 4.37-4.45 (1H, ddd, J = 10.8, 3.2, 2.0 O- $\text{CH}_\text{A}\text{CH}_\text{B}$), 4.64 (1H, td, J = 11.3 3.5 Hz, O- $\text{CH}_\text{A}\text{CH}_\text{B}$), 7.15 (2H, d, J = 7.9 Hz, Ar), 7.27 (3H, td, J = 8.1 Hz, Ar).

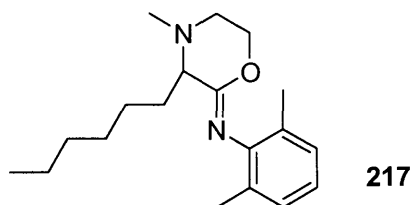
^{13}C NMR (CDCl_3 , 100 MHz) δ 21.2, 43.6, 51.0, 68.4, 72.3, 128.7, 129.3, 134.4, 138.1, 168.9.

HRMS - (FAB (pos)) - calculated for $\text{C}_{12}\text{H}_{16}\text{NO}_2$: 206.11810, found 206.11854.

LRMS – (FAB (pos)) 178 (100), 206 (55, M+H), 176 (17), 179 (13), 207 (8).

IR (thin film) ν max- 2951 (alkyl), 2795 (N- CH_3), 1738 ($\text{C}=\text{O}$ ester), 1514, 1456 cm^{-1} .

(Z)-(2,6-Dimethyl-phenyl)-(3-heptyl-4-methyl-morpholin-2-ylidene)-amine **217**.



Method A

2-Hexyl-3-methyl-oxazolidine **180** (342 mg, 2 mmol), *p*TsOH (8 mg, 0.04 mmol), and then 2,6-dimethylphenyl isocyanide (262 mg, 2 mmol) were added to anhydrous IPA (2 ml) and refluxed under an atmosphere of nitrogen for 17 h. Excess solvent

was removed under reduced pressure and the crude product was purified by column chromatography (10:1 hexanes:EtOAc) to yield *(Z)*-(2,6-Dimethyl-phenyl)-(3-heptyl-4-methyl-morpholin-2-ylidene)-amine **217** as a colourless oil (421 mg, 73 %). R.f. = 0.23 (6:1 hexanes:EtOAc).

Method B

2-Hexyl-3-methyl-oxazolidine **180** (342 mg, 2 mmol), *p*TsOH (8 mg, 0.04 mmol), and then 2,6-dimethylphenyl isocyanide (262 mg, 2 mmol) were added to anhydrous MeOH (2 ml) and heated at reflux under an atmosphere of nitrogen for 6 d. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (8:1 hexanes:EtOAc) to give *(2,6-Dimethyl-phenyl)-(3-heptyl-4-methyl-morpholin-2-ylidene)-amine* **217** as a colourless oil (202 mg, 33 %) and recovery of 2-hexyl-3-methyl-oxazolidine **180** (137 mg, 40 %).

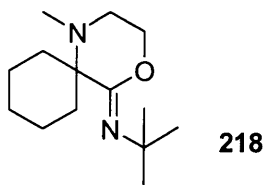
¹H NMR (CDCl₃) δ 0.99 (3H, t, J = 6.4 Hz, CH₂CH₃), 1.33-1.51 (6H, m, alkyl), 1.58-1.74 (2H, m, alkyl), 1.93-2.04 (1H, m, alkyl), 2.17 (6H, s, Ar-CH₃), 2.21-2.34 (1H, m, alkyl), 2.48 (3H, s, N-CH₃), 2.65 (1H, ddd, J = 12.9, 9.4, 3.8 Hz, N-CH_ACH_B), 2.92 (1H, dt, J = 3.5, 12.7 Hz, N-CH_ACH_B), 3.32 (1H, t, J = 4.8 Hz, CH), 4.05-4.22 (2H, m, O-CH₂), 6.83 (1H, t, J = 7.6 Hz, Ar), 7.04 (2H, d, J = 10.4 Hz, Ar).

¹³C NMR (CDCl₃) δ 14.2, 18.9, 22.7, 25.4, 29.7, 31.8, 32.0, 43.5, 51.1, 65.2, 66.4, 122.6, 127.5, 128.3, 145.4, 155.8.

HRMS - (FAB (pos)) - calculated for C₂₀H₃₂N₂NaO: 325.22557, found 325.22509.

LRMS -(FAB (pos)) 325 (100, M+Na), 218 (73), 301 (67), 176 (60), 303 (50), 170 (48).

IR (thin film) ν max- 3021 (aryl), 2957 (alkyl), 2957 (alkyl), 2854 (alkyl), 1624 (C=N), 1477, 1443 cm⁻¹.

(Z)-(tert-Butyl)-1-Methyl-(5-ylidene-4-oxa-1-aza-spiro[5.5]undecane) 218.

4-Methyl-1-oxa-4-aza-spiro[4.5]decane **184** (300 mg, 2 mmol), *p*TsOH (38 mg, 0.2 mmol), and then *tert*-butyl isocyanide (226 μ l, 2 mmol) were added to MeCN (2 ml) and heated to 80°C under an atmosphere of nitrogen for 17 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (2:1 hexanes:EtOAc) to yield the title compound **218** as a colourless oil (153 mg, 32 %). R.f. = 0.24 (2:1 hexanes:EtOAc).

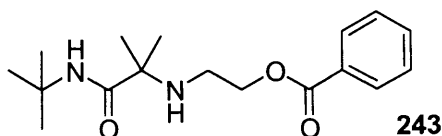
¹H NMR (CDCl₃) δ 1.20 (9H, s, *t*-Bu), 1.32-1.46 (2H, m, CH₂), 1.48-1.58 (4H, m, CH₂), 1.70-1.86 (4H, m, CH₂-C-CH₂), 1.86 (N-CH₃), 3.08 (2H, t, *J* = 5.8 Hz, N-CH₂), 4.15 (2H, t, *J* = 5.8 Hz, O-CH₂).

¹³C NMR (CDCl₃) δ 21.5, 25.9, 30.4, 32.5, 36.6, 46.7, 53.1, 60.2, 63.4, 156.9.

HRMS - (FAB (pos)) - calculated for C₁₄H₂₇N₂O: 239.21234, found 239.21278.

LRMS - (FAB (pos)) 239 (100, M+H), 159 (68), 240 (26), 183 (6), 166 (3), 181 (3).

IR (thin film) ν max- 2934 (alkyl), 2860 (alkyl), 2793 (N-CH₃), 1674 (C=N), 1448, cm⁻¹.

2-(1-tert-Butylcarbamoyl-1-methyl-ethylamino)-ethyl benzoate 243.

2,2-Dimethyl-oxazolidine / 2-(propan-2-ylideneamino)ethanol **187** (202 mg, 2 mmol), benzoic acid (244 mg, 2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μ l, 2

mmol) were added to anhydrous IPA (2 ml) and heated at reflux under an atmosphere of nitrogen for 18 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (1:1 isohexane:EtOAc) to yield *2-(1-tert-butylcarbamoyl-1-methyl-ethylamino)-ethyl benzoate* **243** as a colourless oil (224 mg, 37 %). R.f. = 0.35 (1:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 1.27 (9H, s, *t*-Bu), 1.28 (6H, s, CH₃), 2.86 (2H, t, J= 5.5 Hz, N-CH₂), 4.37 (2H, t, J= 5.6 Hz, O-CH₂), 7.13 (1H, bs, NH), 7.43 (2H, t, J= 7.5 Hz, *m*-Ar), 7.52 (1H, m, *p*-Ar), 8.01 (2H, d, J= 10.0 Hz, *o*-Ar).

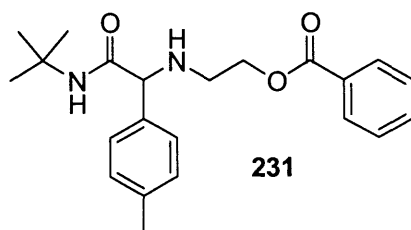
¹³C NMR (CDCl₃) δ 25.6, 28.6, 42.6, 50.1, 58.9, 65.0, 128.4, 129.6, 130.0, 133.1, 166.6, 175.6.

HRMS - (CI (pos) methane) - Measured (M+H) = 307.20284, theoretical (M+H) = 307.20216.

LRMS - (CI (pos) methane) 206 (100), 307 (63, M+H), 111 (16), 149 (15), 113 (15), 207 (14).

IR (thin film) ν max- 3330 br (NH), 2995(alkyl), 2940 (alkyl), 2880 (alkyl), 1720 (C=O), 1665 (C=O), 1510 (NH), 1406 cm⁻¹.

2-[(tert-Butylcarbamoyl-p-tolyl-methyl)-amino]-ethyl benzoate **231**.



2-p-Tolyl-oxazolidine / 2-[(4-methyl-benzylidene)-amino]-ethanol **186** (326 mg, 2 mmol), benzoic acid (244 mg, 2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μl, 2 mmol) were added to anhydrous IPA (2 ml) and heated at reflux under an atmosphere of nitrogen for 18 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1

isohexane:EtOAc) to yield 2-[(*tert*-butylcarbamoyl-*p*-tolyl-methyl)-methylamino] ethyl propionate **231** as a colourless oil (516 mg, 70 %). R.f. = 0.36 (2:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 1.28 (9H, s, *t*-Bu), 2.07 (1H, bs, NH), 2.28 (3H, s, tolyl-CH₃), 2.88-3.02 (2H, m, N-CH₂), 4.08 (1H, s, CH), 4.34-4.41 (2H, m, O-CH₂), 6.96 (1H, s, NH), 7.10 (2H, d, J= 7.8 Hz, Ar), 7.22 (2H, d, J= 8.1 Hz, Ar), 7.38-7.55 (3H, m, Ar), 8.00 (2H, d, J= 8.3 Hz, Ar).

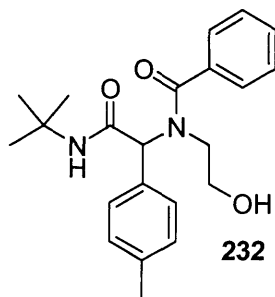
¹³C NMR (CDCl₃) δ 21.1, 28.7, 47.1, 50.6, 64.3, 67.7, 126.8, 128.4, 129.1, 129.5, 130.0, 133.1, 136.6, 137.7, 166.5, 171.2.

HRMS - (FAB (pos)) - calculated for C₂₂H₂₉N₂O₃: 369.21781, found 369.21690.

LRMS – (FAB (pos)) 369 (100, M+H), 268 (61), 370 (27), 154 (23), 176 (13).

IR (thin film) ν max- 3370 br (NH), 2985 (alkyl), 2930 (alkyl), 2880 (alkyl), 1716 (C=O), 1670 (C=O), 1514 (NH), 1452 cm⁻¹.

N-(*tert*-Butylcarbamoyl-*p*-tolyl-methyl)-*N*-(2-hydroxy-ethyl)-benzamide **232**.



2-*p*-Tolyl-oxazolidine **186** (327 mg, 2 mmol), benzoic acid (244 mg, 2 mmol), and then *tert*-butyl isocyanide (2 mmol 226 μl) were added to anhydrous methanol (5 ml) at r.t and stirred for 42 h under an atmosphere of nitrogen. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (2:1 hexanes:EtOAc) to yield *N*-(*tert*-butylcarbamoyl-*p*-tolyl-methyl)-*N*-(2-hydroxy-ethyl)-benzamide **232** (660 mg, 90 %) as a white powder. R.f =

0.16 (2:1 hexanes:EtOAc). Recrystallised from petrol / IPA to give colourless needles (m.p. = 138-139°C).

¹H NMR (DMSO d₆, 400 MHz, 373K) δ 1.35 (9H, s, *t*-Bu), 2.33 (3H, s, tolyl-CH₃), 3.13-3.27 (2H, m, N-CH₂), 3.39-3.49 (2H, m, O-CH₂), 4.45 (1H, bs, OH), 5.58 (1H, s, CH), 7.20-7.26 (4H, m, Ar), 7.38 (1H, bs, NH), 7.43-7.48 (5H, m, Ar).

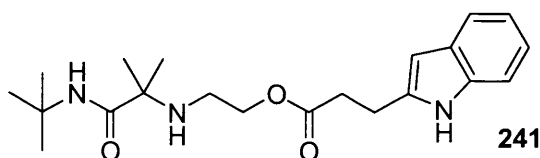
¹³C NMR (DMSO d₆, 100 MHz 373K) δ 19.9, 27.9, 47.5, 50.1, 58.6, 63.9, 125.9, 127.6, 128.34, 128.40, 128.5, 132.9, 136.6, 136.7, 168.5, 171.5.

HRMS - (EI) - calculated for C₂₂H₂₉N₂O₃: 369.21782, found 369.21828.

LRMS - (EI) 369 (100 M+H), 367 (92, M+Na), 370 (30), 396 (29), 392 (27), 268 (10).

IR (KBr Disc) ν max- 3406 br, 3317, 3027 (aryl), 2993 (alkyl), 2981 (alkyl), 2931 (alkyl), 1665 (C=O amide), 1618 (C=O amide), 1542, 1450, 1419 cm⁻¹.

3-(1*H*-Indol-3-yl)-2-(1-*tert*-butylcarbamoyl-1-methyl-ethylamino)-ethyl ester **241**.



2,2-Dimethyl-oxazolidine / 2-(propan-2-ylideneamino)ethanol **187** (202 mg, 2 mmol), 3-indolepropionic acid (379 mg, 2 mmol) and then *tert*-butyl isocyanide (166 mg / 226 μl, 2 mmol) were added to anhydrous IPA (2 ml) and heated at reflux under an atmosphere of nitrogen for 18 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (50:50:1 isohehexane: EtOAc:TEA) to yield 3-(1*H*-Indol-3-yl)-2-(1-*tert*-butylcarbamoyl-1-methyl-ethylamino)-ethyl ester **241** as a colourless oil (284 mg, 38 %). R.f.= 0.11 (50:50:1 isohehexane:EtOAc:TEA).

¹H NMR (CDCl₃) δ 1.22 (6H, s, (CH₃)₂), 1.27 (9H, s, *t*-Bu), 2.04 (1H, s, NH), 2.67 (2H, t, J= 5.5 Hz, N-CH₂), 2.75 (2H, t, J= 7.5 Hz, CO-CH₂), 3.12 (2H, t, J= 7.5 Hz, Indole-CH₂), 3.61-4.36 (2H, m, O-CH₂), 7.00 (1H, d, J= 2.2 Hz, Ar), 7.11-7.22 (2H, m, Ar), 7.28 (1H, bs, NH amide), 7.34 (1H, d, J= 8.0 Hz, Ar), 7.59 (1H, d, J= 7.7 Hz, Ar), 8.51 (1H, bs, NH indole).

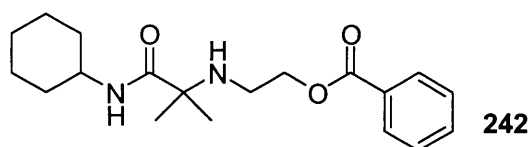
¹³C NMR (CDCl₃) δ 20.7, 25.5, 28.7, 34.9, 42.3, 50.1, 58.8, 64.5, 111.3, 114.5, 118.6, 119.2, 121.6, 122.0, 127.1, 136.4, 173.4, 175.6.

HRMS - (ES (pos)) - calculated for C₂₁H₃₂N₃O₃: 374.24437, found 374.24483.

LRMS - (ES (pos)) 374 (100 M+H), 273 (35), 375 (22), 396 (16), 203 (8), 274 (7).

IR (KBr Disc) ν max- 3354 (NH), 3318 (NH), 3171 (NH), 2974 (alkyl), 2923 (alkyl), 1730 (C=O ester), 1645 (C=O amide), 1521, 1456 cm⁻¹.

2-(1-Cyclohexylcarbamoyl-1-methyl-ethylamino)-ethyl benzoate 242.



2,2-Dimethyl-oxazolidine / 2-(propan-2-ylideneamino)ethanol **187** (202 mg, 2 mmol), benzoic acid (244 mg, 2 mmol) and then cyclohexyl isocyanide (249 μl, 2 mmol) were added to anhydrous IPA (2 ml) and heated at reflux under an atmosphere of nitrogen for 18 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (4:1 isohexane:EtOAc) to yield 2-(1-cyclohexylcarbamoyl-1-methyl-ethylamino)-ethyl benzoate **242** as a yellow oil (258 mg, 37 %). R.f.= 0.19 (Et₂O).

¹H NMR (CDCl₃) δ 0.83-1.04 (4H, m, cy), 1.27 (6H, s, (CH₃)₂), 1.44-1.61 (4H, m, cy), 2.83 (2H, t, J= 5.4 Hz, N-CH₂), 3.56-3.64 (1H, tdt, J= 10.6, 8.9, 3.9 Hz, cy H_(ax)),

4.35 (2H, t, $J = 5.4$ Hz, O-CH₂), 7.21 (1H, br d, $J = 8.4$ Hz, CONH), 7.41 (2H, tt, $J = 7.4, 1.3$ Hz, Ar), 7.53 (1H, tt, $J = 7.4, 1.3$ Hz, Ar), 8.00 (2H, d, $J = 8.5$ Hz, Ar)

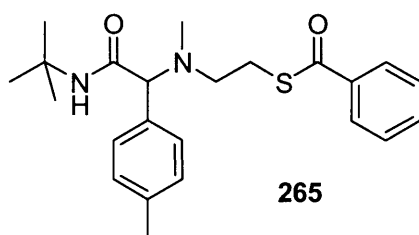
¹³C NMR (CDCl₃) δ 24.8, 25.5, 25.7, 33.0, 42.7, 47.5, 58.5, 64.9, 128.4, 129.6, 130.0, 133.1, 166.5, 175.2.

HRMS - (EI) - calculated for C₁₉H₂₉N₂O₃: 333.21782, found 333.21810.

LRMS - (EI) 333 (100 M+H), 355 (61, M+Na), 206 (37), 334 (17), 356 (11), 207 (5).

IR (thin film) ν max- 3320 br (NH), 2930 (alkyl), 2871 (alkyl), 1720 (C=O ester), 1661 (C=O amide), 1514, 1463 cm⁻¹.

S-{2-[(*tert*-Butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]-ethyl} thiobenzoate **245**.



3-Methyl-2-*p*-tolyl-oxazolidine **179** (355 mg, 2 mmol), thiobenzoic acid (259 μ l, 2 mmol), *p*TsOH (19 mg, 0.1 mmol) and *tert*-butyl isocyanide (166 mg, 226 μ l, 2 mmol) were added to anhydrous MeCN (5 ml) and heated at reflux under an atmosphere of argon for 24 h. Excess solvent was removed under reduced pressure. Purification by column chromatography (4:1 isohexane:EtOAc) afforded *S*-{2-[(*tert*-butylcarbamoyl-*p*-tolyl-methyl)-methyl-amino]-ethyl} thiobenzoate **245** as a pale yellow oil (159 mg, 20 %). R.f. = 0.33 (2:1 isohexane:EtOAc).

¹H NMR (CDCl₃, 400 MHz) δ 1.24 (9H, s, *t*-Bu), 2.15 (3H, s, N-CH₃), 2.22 (3H, s, Ar-CH₃), 1.02 (2H, t, $J = 6.7$ Hz, N-CH₂), 3.09-3.21 (2H, m, S-CH₂), 3.81 (1H, bs, NH), 7.02 (2H, d, $J = 8.0$ Hz, Ar), 7.09 (2H, d, $J = 8.0$ Hz, Ar), 7.34-7.38 (2H, m, Ar), 7.47-7.51 (1H, m, Ar), 7.87-7.89 (2H, m, Ar).

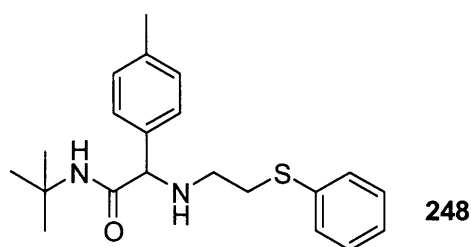
^{13}C NMR (CDCl_3 , 100 MHz) δ 21.5, 27.6, 29.0, 39.9, 51.0, 54.5, 75.5, 127.1, 128.5, 128.9, 130.0, 132.8, 133.4, 136.8, 137.5, 170.5, 191.2.

HRMS - (FAB (pos)) - calculated for $\text{C}_{23}\text{H}_{31}\text{N}_2\text{O}_2\text{S}_2$: 399.2106, found 399.2109.

LRMS – (FAB (pos)) 399 (100, $\text{M}+\text{H}$), 400 (22), 397 (4), 291 (2), 260 (1), 176 (1).

IR (thin film) ν max- 3444 br (NH), 3007 (aryl), 2970 (alkyl), 2898 (alkyl), 1667 ($\text{C}=\text{O}$), 1662 ($\text{C}=\text{S}$), 1506 (NH), 1470 cm^{-1} .

N-tert-Butyl-2-(2-phenylsulfanyl-ethylamino)-2-*p*-tolyl-acetamide **248**.



2-*p*-Tolyl-oxazolidine **186** (163 mg, 2 mmol), thiophenol (205 μl , 2 mmol), *p*TsOH (19 mg, 0.1 mmol) and *tert*-butyl isocyanide (166 mg, 226 μl , 2 mmol) were added to anhydrous MeCN (2 ml) and heated at reflux under an atmosphere of nitrogen for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (2:1 hexanes:EtOAc) to yield *N*-tert-butyl-2-(2-phenylsulfanyl-ethylamino)-2-*p*-tolyl-acetamide **248** as a colourless oil (40 mg, 6 %). R.f. = 0.19 (2:1 hexanes:EtOAc).

^1H NMR (CDCl_3) δ 1.32 (9H, s, *t*-Bu), 1.91-2.04 (1H, bs, NH), 2.37 (3H, s, Ar-CH₃), 2.84 (2H, m, S-CH₂), 3.02-3.08 (2H, m, NH-CH₂), 3.97 (1H, s, CH), 7.13- 7.37 (9H, m, Ar).

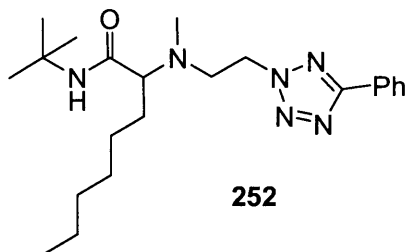
^{13}C NMR (CDCl_3) δ 21.2, 28.7, 34.5, 47.2, 67.7, 126.4, 127.0, 129.0, 129.5, 129.7, 131.8, 136.7, 137.6, 171.2.

HRMS - (ES (pos)) - calculated for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{OS}$: 357.20006, found 357.20142.

LRMS – (ES (pos)) 357 (100, M+H), 379 (74, M+Na), 176 (73), 256 (30), 358 (27).

IR (thin film) ν max- 3330 br (NH), 2974 (alkyl), 2905 (alkyl), 2865 (alkyl), 1662 (C=O amide), 1515, 1480, 1454 cm^{-1} .

2-{Methyl-[2-(5-phenyl-tetrazol-1-yl)-ethyl]-amino}-octanoic acid tert-butylamide
252.



2-Hexyl-3-methyl-oxazolidine **180** (343 mg, 2 mmol), 5-phenyl-1*H*-tetrazole (292 mg, 2 mmol), *p*TsOH (19 mg, 0.1 mmol) and then *tert*-butyl isocyanide (226 μl , 2 mmol) were added to anhydrous MeCN (5 ml) at r.t. and then heated at reflux under an atmosphere of nitrogen for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (80:10:1 hexanes:EtOAc:TEA) to yield 2-{Methyl-[2-(5-phenyl-tetrazol-1-yl)-ethyl]-amino}-octanoic acid *tert*-butylamide **252** as a colourless oil (565 mg, 71 %). R.f. = 0.35 (90:30:1 hexanes:EtOAc:TEA).

^1H NMR (CDCl_3) δ 0.74 (3H, t, J = 6.8 Hz, CH_2CH_3), 1.11 (9H, s, t-Bu), 1.16-1.28 (8H, m, alkyl), 1.33-1.44 (1H, m, alkyl), 1.57-1.68 (1H, m, alkyl), 2.17 (3H, s, N- CH_3), 2.76 (1H, dd, J = 7.1, 5.8 Hz, CH), 3.03 (1H, ddd, J = 13.6, 7.0, 5.2 Hz, $\text{CH}_3\text{NCH}_\text{A}\text{CH}_\text{B}$), 3.13 (1H, ddd, J = 13.6, 7.0, 5.2 Hz, $\text{CH}_3\text{NCH}_\text{A}\text{CH}_\text{B}$), 4.58 (1H, ddd, J = 13.9, 7.0, 5.2 Hz, N- $\text{CH}_\text{A}\text{CH}_\text{B}$), 4.67 (1H, ddd, J = 13.9, 7.0, 5.1 Hz, N- $\text{CH}_\text{A}\text{CH}_\text{B}$), 6.26 (1H, s, NH), 7.31-7.39 (3H, m, Ar), 8.00-8.05 (2H, m, Ar).

^{13}C NMR (CDCl_3) δ 14.0, 22.5, 27.0, 27.4, 28.5, 29.2, 31.6, 37.3, 50.3, 51.3, 53.9, 68.6, 126.7, 127.3, 128.8, 130.3, 165.0, 171.6.

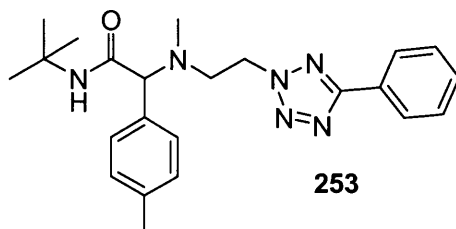
HRMS - (CI (pos-methane)) - calculated for $C_{22}H_{37}N_4O$: 401.30287, found 401.30378.

LRMS – (CI (pos-methane)) 401 (100, M+H), 300 (80), 104 (53), 402 (26), 255 (23), 272 (20).

IR (thin film) ν max- 3335 br (NH), 2955 (alkyl), 2920 (alkyl), 2862 (alkyl), 1665 (C=O amide), 1518 (NH), 1460 cm^{-1} .

N-tert-Butyl-2-(methyl(2-(5-phenyl-2H-tetrazol-2-yl)ethyl)amino)-2-p-tolylacetamide

253.



3-Methyl-2-*p*-tolyl-oxazolidine **179** (355 mg, 2 mmol), 5-phenyl-1*H*-tetrazole (292 mg, 2 mmol), *p*TsOH (19 mg, 0.1 mmol) and then *tert*-butyl isocyanide (226 μl , 2 mmol) were added to anhydrous MeCN (5 ml) at r.t. and then heated at reflux under an atmosphere of nitrogen for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (80:10:1 hexanes:EtOAc:TEA) to yield *N-tert-butyl-2-(methyl(2-(5-phenyl-2H-tetrazol-2-yl)ethyl)amino)-2-p-tolylacetamide* **253** as a colourless oil (441 mg, 67 %). R.f. = 0.11 90:30:1 (hexanes:EtOAc:TEA).

^1H NMR (CDCl_3) δ 1.56 (9H, s, t-Bu), 2.26 (3H, s, N-CH₃), 2.33 (3H, s, tolyl-CH₃), 2.85-2.92 (1H, m, CH₃NCH_ACH_B), 2.99 (1H, m, CH₃NCH_ACH_B), 3.84 (1H, s, CH), 4.62-4.68 (1H, m, N-CH_ACH_B), 4.72-4.81 (1H, m, N-CH_ACH_B), 6.61 (1H, s, NH), 6.92 (2H, d, J= 8.2 Hz, Ar), 7.02 (2H, d, J= 7.8 Hz, Ar), 7.49-7.60 (3H, m, Ar), 8.13-8.16 (2H, m, Ar).

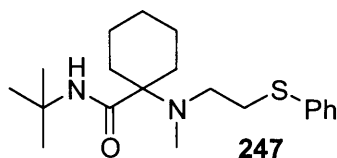
^{13}C NMR (CDCl_3) δ 21.1, 28.5, 40.1, 50.7, 51.1, 53.1, 75.4, 126.8, 127.4, 128.8, 128.9, 129.3, 130.4, 132.6, 137.9, 165.2, 170.3.

HRMS - (ES (pos)) - calculated for $\text{C}_{23}\text{H}_{31}\text{N}_2\text{O}$: 407.25593, found 407.25580.

LRMS - (ES (pos)) 407 (100, $\text{M}+\text{H}$), 429 (39, $\text{M}+\text{Na}$), 408 (26), 430 (8), 379 (7).

IR (thin film) ν max- 3190 (br, NH), 2966, 2873, 1668 ($\text{C}=\text{O}$ amide), 1514, 1466, 1452 cm^{-1} .

1-[Methyl-(2-phenylsulfanyl-ethyl)-amino]-cyclohexanecarboxylic acid tert-butylamide 247.



4-Methyl-1-oxa-4-aza-spiro[4.5]decane **184** (311 mg, 2 mmol), thiophenol (205 μl , 2 mmol), *p*TsOH (19 mg, 0.1 mmol) and then *tert*-butyl isocyanide (166 mg, 226 μl , 2 mmol) were added to anhydrous MeCN (1 ml) and heated at reflux under an atmosphere of nitrogen for 24 h. Excess solvent was removed under reduced pressure and the crude product was purified by column chromatography (6:1 hexanes:EtOAc) to yield *1-[Methyl-(2-phenylsulfanyl-ethyl)-amino]-cyclohexanecarboxylic acid tert-butylamide 247* as a colourless oil (154 mg, 22 %). R.f. = 0.40 (6:1 hexanes:EtOAc).

^1H NMR (CDCl_3) δ 1.32 (9H, s, *t*-Bu), 1.39-1.77 (10H, m, cyclohexyl), 2.23 (3H, s, N- CH_3), 2.70 (2H, dd, J = 7.7 6.7 Hz, N- CH_2), 3.03 (2H, dd, J = 7.7 6.7 Hz, S- CH_2), 6.71 (1H, bs, NH), 7.14-7.34 (4H, m, Ar).

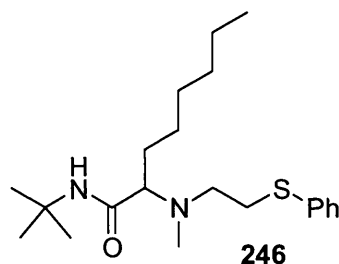
^{13}C NMR (CDCl_3) δ 23.0, 26.0, 28.7, 30.3, 33.5, 34.5, 66.6, 125.9, 128.9, 129.0, 136.8, 175.6.

HRMS - (CI (pos) methane) - calculated for $\text{C}_{20}\text{H}_{33}\text{N}_2\text{OS}$: 349.23135, found 349.23170.

LRMS – (CI (pos) methane) 248 (100), 349 (74, M+H), 137 (30), 249 (17), 350 (16), 347 (15).

IR (thin film) ν max- 3380 br (NH), 2959 (alkyl), 2930 (alkyl), 1676 (C=O), 1508, 1481, 1448 cm^{-1} .

2-[Methyl-(2-phenylsulfanyl-ethyl)-amino]-octanoic acid tert-butylamide **246**.



2-Hexyl-3-methyl-oxazolidine **180** (342 mg, 2 mmol), thiophenol (205 μl , 2 mmol), *p*TsOH (19 mg, 0.1 mmol) and then *tert*-butyl isocyanide (166 mg, 226 μl , 2 mmol) were added to anhydrous MeCN (1 ml) and heated at reflux under an atmosphere of nitrogen for 24 h. Excess solvent was removed under reduced pressure and the residue was purified by column chromatography (8:1 hexanes:EtOAc) to yield 2-[Methyl-(2-phenylsulfanyl-ethyl)-amino]-octanoic acid *tert*-butylamide **246** as a colourless oil (428 mg, 59 %). R.f. = 0.21 (6:1 hexanes:EtOAc).

^1H NMR (CDCl_3) δ 0.81 (3H, t, J = 6.7 Hz, CH_2CH_3), 1.21 (7H, bs, alkyl), 1.28 (9H, s, *t*-Bu), 1.34-1.59 (2H, m, alkyl), 1.64-1.73 (1H, m, alkyl), 2.19 (3H, s, N- CH_3), 2.71 (2H, t, J = 6.6 Hz, N- CH_2), 2.81 (1H, dd, J = 7.1, 5.5 Hz, CH), 2.99 (2H, t, J = 6.6 Hz, S- CH_2), 7.10-7.29 (4H, m, Ar).

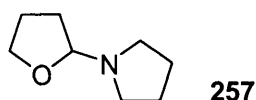
^{13}C NMR (CDCl_3) δ 14.1, 22.6, 27.2, 27.5, 28.7, 29.2, 29.5, 31.7, 32.7, 37.4, 50.4, 53.7, 68.7, 126.0, 127.4, 128.9, 129.2, 136.4, 172.4.

HRMS - (CI (pos) methane) - calculated for $\text{C}_{21}\text{H}_{37}\text{N}_2\text{OS}$: 365.26265, found 365.26202.

LRMS – (CI (pos) methane) 111 (100), 255 (32), 156 (28), 365 (20, M+H), 257 (20), 128 (17).

IR (thin film) ν max- 3430 br (NH), 2958 (alkyl), 2927 (alkyl), 2856 (alkyl), 1674 (C=O), 1510 (NH), 1481, 1456 cm^{-1} .

1-(Tetrahydrofuran-2-yl)pyrrolidine **257**.



The title compound **257** was prepared following a standard literature procedure.¹⁵⁰

To a stirred mixture of 2,3-dihydrofuran (22.5 ml, 297 mmol) and pyrrolidine (2.2 ml, 26.1 mmol) at r.t. was added potassium *tetrakis*(thiocyanate)palladium(II) (234 mg, 0.54 mmol) the mixture was stirred at 80°C for 18 h. The volatile reagents were then removed under reduced pressure. Hexanes (90 ml) were then added and the mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was distilled under reduced pressure (80-83°C, 6 mm/Hg), (lit¹⁵⁰ = 65-67°C, 4.5 mm/Hg) to give 1-(tetrahydrofuran-2-yl)pyrrolidine **257** as a colourless oil (2.80 g, 76 %).

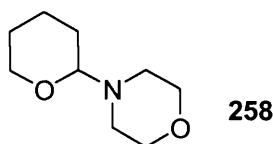
¹H NMR (CDCl_3) δ 1.73-2.02 (8H, m, CH_2), 2.63-2.82 (4H, m, $\text{CH}_2\text{-N-CH}_2$), 3.79-3.93 (2H, m, O- CH_2), 4.76 (1H, t, $J = 5.6$ Hz, O-CH).

¹³C NMR (CDCl_3) δ 23.8, 25.5, 30.0, 47.9, 67.1, 93.5.

LRMS – (CI (pos) methane) 97 (100), 111 (64), 125 (55), 96 (35), 98 (34), 113 (27).

IR (thin film) ν max- 2964 (alkyl), 2872 (alkyl), 1456, 1402 cm^{-1} .

4-(Tetrahydro-2H-pyran-2-yl)morpholine **258**.



The title compound **258** was prepared following a standard literature procedure.¹⁵⁰ To a stirred mixture of 2,3-dihydropyran (9.1 ml, 100 mmol) and morpholine (721 μ l, 8.7 mmol) at r.t. was added potassium *tetrakis*(thiocyanate)palladium(II) (78 mg, 0.18 mmol) the mixture was stirred at 80°C for 18 h. The volatile reagents were then removed under reduced pressure. Hexanes (30 ml), were then added and the mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was distilled under reduced pressure (90-92°C, 4 mm/Hg), (lit¹⁵⁰ = 111.5°C, 12 mm/Hg) to give 4-(tetrahydro-2*H*-pyran-2-yl)morpholine **258** as a colourless oil (1.43 g, 96 %).

¹H NMR (CDCl₃) δ 1.40-1.64 (5H, m, CH₂), 1.80-1.93 (1H, m, CH), 2.54-2.62 (2H, m, N-CH₂), 2.82-2.90 (2H, m, CH₂), 3.36-3.47 (1H, m, O-CH), 3.63-3.79 (4H, CH₂-O-CH₂), 3.96 (1H, dd, J=11.1, 3.0 Hz, O-CH).

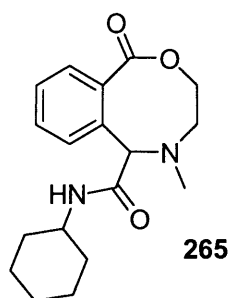
¹³C NMR (CDCl₃) δ 23.4, 25.8, 28.4, 48.2, 67.2, 67.5, 93.6.

HRMS - (EI) - calculated for C₉H₁₇NO₂: 171.12592, found 171.12534.

LRMS - (EI) 85 (100), 113 (87), 119 (65), 225 (41), 171 (64, M⁺), 149 (63).

IR (thin film) ν max- 2955 (alkyl), 2861 (alkyl), 1403 cm⁻¹.

5-Methyl-1-oxo-3,4,5,6-tetrahydro-1*H*-benzo[*ff*][1,4]oxazocine-6-carboxylic acid cyclohexylamide **265**.



2-(Methylamino)-ethanol (161 μ l, 2 mmol), *p*TsOH (8 mg, 0.04 mmol), and cyclohexyl isocyanide (202 μ l, 2 mmol) were added to a solution of 2-carboxybenzaldehyde (300 mg, 2 mmol) in anhydrous IPA (1.5 ml). The mixture was

stirred for 48 h at r.t. under N₂. Excess solvent was removed under reduced pressure and the residue was purified by flash chromatography (2:1 hexanes:EtOAc) to give 5-methyl-1-oxo-3,4,5,6-tetrahydro-1H-benzo[f][1,4]oxazocine-6-carboxylic acid cyclohexylamide **265** as a white solid, which was recrystallised from Methanol to give colourless needles (202 mg, 33 %), (m.p. = 146-148°C) R.f. = 0.12 (2:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 1.08-1.37 (5H, m, cy), 1.51-1.88 (5H, m, cy), 2.32 (3H, s, N-CH₃), 2.94 (1H, ddd, J= 14.2, 7.3, 3.8 Hz, N-CH_ACH_B), 3.07 (1H, ddd, J= 14.2, 4.0, 3.8 Hz, N-CH_ACH_B), 3.69 (1H, dtd, J= 10.5, 8.5, 3.9 Hz, cy), 3.84 (1H, ddd, J= 12.6, 5.8, 3.8 Hz, O-CH_ACH_B), 4.07 (1H, ddd, J= 12.6, 7.3, 4.0 Hz, O-CH_ACH_B), 4.27 (1H, s, CH), 6.96 (d, J= 8.2 Hz, NH), 7.04-7.06 (1H, m, Ar), 7.28-7.32 (3H, m, Ar).

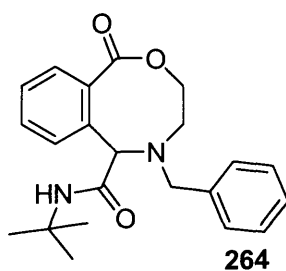
¹³C NMR (CDCl₃) δ 24.6, 25.4, 32.7, 32.9, 42.4, 48.1, 55.5, 64.8, 70.6, 128.3, 128.6, 130.2, 130.8, 134.9, 168.3, 173.4.

HRMS - (EI) -calculated for C₁₈H₂₅N₂O₃: 317.18652, found 317.18574.

LRMS - (EI) 339 (100 M+Na), 317 (83, M+H), 340 (17), 318 (13), 202 (12), 221 (7).

IR (KBr Disc) ν max- 3309 (NH), 2936 (alkyl), 2854 (alkyl), 1717 (ester), 1634 (C=O amide), 1539, 1454 cm⁻¹.

5-Benzyl-1-oxo-3,4,5,6-tetrahydro-1H-benzo[f][1,4]oxazocine-6-carboxylic acid tert-butylamide **264**.



2-(Benzylamino)-ethanol (284 μ l, 2 mmol), pTsOH (8 mg, 0.04 mmol), and *tert*-butyl isocyanide (226 μ l, 2 mmol) were added to a solution of 2-carboxybenzaldehyde (300 mg, 2 mmol) in anhydrous IPA (1.5 ml). The mixture was stirred for 7 days at r.t. under N₂. Excess solvent was removed in *vacuo* and the residue was purified by flash chromatography (3:2 hexanes:EtOAc) to give *5-benzyl-1-oxo-3,4,5,6-tetrahydro-1H-benzo[f][1,4]oxazocine-6-carboxylic acid tert-butylamide* **264** as a pale yellow oil (179 mg, 25 %). R.f. = 0.40 (1:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 1.29 (9H, s, t-Bu), 2.82 (1H, (1H, ddd, J= 14.2, 6.2, 4.2 Hz, N-CH_ACH_B), 3.19 (1H, ddd, J= 14.2, 6.7, 4.8 Hz, N-CH_ACH_B), 3.78 (2H, s, Ar-CH₂), 3.88 (1H, ddd, J= 12.5, 6.8, 4.2 Hz, O-CH_ACH_B), 4.11 (1H, ddd, J= 12.4, 6.3, 4.8, Hz, O-CH_ACH_B), 4.41 (1H, s, CH), 6.42 (1H, bs, NH), 7.29-7.42 (9H, m, Ar).

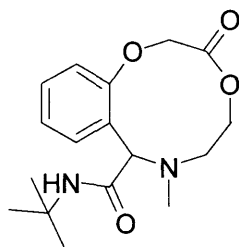
¹³C NMR (CDCl₃) δ 28.5, 51.5, 51.8, 56.9, 64.9, 71.0, 127.3, 127.7, 128.4, 128.4, 128.7, 128.9, 129.1, 130.2, 130.8, 134.4, 137.5, 168.9, 173.7.

HRMS - (EI) – calculated for C₂₂H₂₇N₂O₃: 367.20217, found 367.20211.

LRMS – (EI) 389 (100 M+Na), 367 (64, M+H), 390 (23), 369 (9), 368 (8), 181 (7).

IR (thin film) ν max- 3340 br (NH), 2984 (alkyl), 2924 (alkyl), 2885 (alkyl), 1716 (C=O ester), 1667 (C=O amide), 1486, 1408 cm⁻¹.

11-Methyl-7-oxo-6,7,9,10,11,12-hexahydro-5,8-dioxo-11-aza-benzocyclodecene-12-carboxylic acid tert-butylamide **270**.



2-(Methylamino)-ethanol (161 μ l, 2 mmol), pTsOH (8 mg, 0.04 mmol), and *tert*-butyl isocyanide (226 μ l, 2 mmol) were added to a solution of 2-formylphenoxyacetic acid (360 mg, 2 mmol) in anhydrous IPA (1.5 ml). The mixture was stirred for 48 h

at r.t. Excess solvent was removed under reduced pressure and the residue was purified by flash chromatography (1:1 hexanes:EtOAc) to give *11-methyl-7-oxo-6,7,9,10,11,12-hexahydro-5,8-dioxo-11-aza-benzocyclodecene-12-carboxylic acid tert-butylamide* **270** as a white solid which was recrystallised from IPA to give colourless prisms (317 mg, 49 %), (m.p. = 140-143°C), R.f. = 0.20 (1:1 hexanes:EtOAc).

¹H NMR (CDCl₃) δ 1.30 (9H, s, t-Bu), 2.44 (3H, s, N-CH₃), 2.53 (1H, dt, J= 2.3, 15.5 Hz, N-CH_ACH_B), 2.71-2.82 (1H, m, N-CH_ACH_B), 4.24 (2H, dd, J= 1.7, 6.9Hz, O-CH₂), 4.40 (1H, d, J= 13.4 Hz, OCH_ACH_BC=O), 4.58 (1H, d, J= 13.4 Hz, OCH_ACH_BC=O), 4.79 (1H, s, CH), 6.66 (1H, bs, NH), 6.98-7.07 2H, m, Ar), 7.18 (1H, td, J= 7.7, 1.6 Hz, Ar), 7.26 (1H, dd, J= 7.6, 1.4 Hz, Ar).

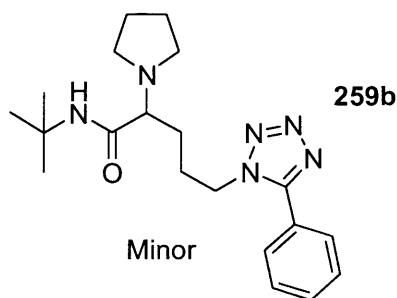
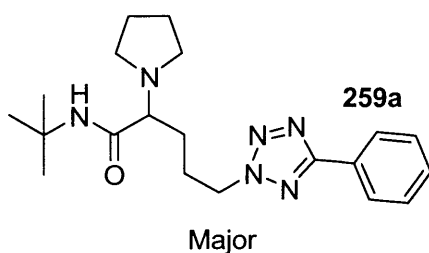
¹³C NMR (CDCl₃) δ 28.6, 38.8, 50.4, 50.6, 60.6, 66.8, 72.8, 121.2, 124.5, 128.6, 129.5, 130.9, 156.8, 168.1, 171.1.

HRMS - (EI) -calculated for C₁₇H₂₅N₂O₄: 321.18143, found 321.18214.

LRMS - (EI) 321 (100 M+H), 322 (18), 343 (10, M+Na), 220 (7), 276 (5), 298 (4).

IR (KBr Disc) ν max- 3356 (NH), 2944 (alkyl), 1742 (C=O ester), 1674 (C=O amide), 1508, 1487, 1448 cm⁻¹.

N-tert-Butyl-5-(5-phenyl-2H-tetrazol-2-yl)-2-(pyrrolidin-1-yl) pentanamide **259a** and *N-tert-butyl-5-(5-phenyl-1H-tetrazol-1-yl)-2-(pyrrolidin-1-yl) pentanamide* **259b** (15:1 Mixture).



1-(Tetrahydrofuran-2-yl)pyrrolidine **257** (282 mg, 2 mmol), 5-phenyl-1H-tetrazole (292 mg, 2 mmol), *p*TsOH (8 mg, 0.04 mmol) and then *tert*-butyl isocyanide (226 μl,

2 mmol) were added to anhydrous MeCN (2ml) and heated at reflux for 42 h under an atmosphere of N₂. Excess solvent was removed under reduced pressure and the residue was purified by flash column chromatography (2:1 hexanes:EtOAc).to give *N-tert-Butyl-5-(5-phenyl-2H-tetrazol-2-yl)-2-(pyrrolidin-1-yl) pentanamide* **259a** and *N-tert-Butyl-5-(5-phenyl-1H-tetrazol-1-yl)-2-(pyrrolidin-1-yl) pentanamide* **259b** (15:1 mixture) as a colourless oil (548 mg, 74%). R.f. = 0.23 (2:1 hexanes:EtOAc).

Major regioisomer ¹H NMR (CDCl₃, 500 MHz) δ 1.28 (9H, s, t-Bu), 1.48-1.57 (1H, m, CHCH_AH_B), 1.65-1.69 (4H, m, CH₂-CH₂), 1.69-1.77 (1H, m, CHCH_AH_B), 2.01-2.08 (1H, m, CH_AH_B), 2.08-2.18 (1H, m, CH_AH_B), 2.38-2.44 (4H, m, CH₂-N-CH₂), 2.62 (1H, dd, J= 8.7, 4.3 Hz, CH), 4.60 (1H, ddd, J= 13.6, 8.2, 6.9 Hz, N-CH_AH_B), 4.64 (1H, ddd, J= 13.6, 8.2, 6.9, Hz, N-CH_AH_B), 6.54 (1H, bs, NH), 7.38-7.42 (3H, m, Ar), 8.06 (2H, dd, J= 8.2, 1.9 Hz, Ar).

¹³C NMR (CDCl₃, 125 MHz) δ 23.06, 25.3, 28.46, 28.53, 51.3, 52.7, 60.13, 68.9, 126.6, 127.3, 128.7, 130.0, 164.8, 171.83.

Minor regioisomer ¹H NMR (CDCl₃, 500 MHz) δ 1.24 (9H, s, t-Bu), 1.48-1.57 (1H, m, CH₂), 1.48-1.57 (1H, m, CHCH_AH_B), 1.65-1.69 (4H, m, CH₂-CH₂), 1.69-1.77 (1H, m, CHCH_AH_B), 2.01-2.08 (1H, m, CH_AH_B), 2.08-2.18 (1H, m, CH_AH_B), 2.38-2.44 (4H, m, CH₂-N-CH₂), 2.52 (1H, dd, J= 8.8, 4.5 Hz, CH), 4.38-4.43 (2H, m, N-CH₂), 6.52 (1H, bs, NH), 7.46-7.50 (3H, m, Ar), 7.61-7.65 (2H, m, Ar).

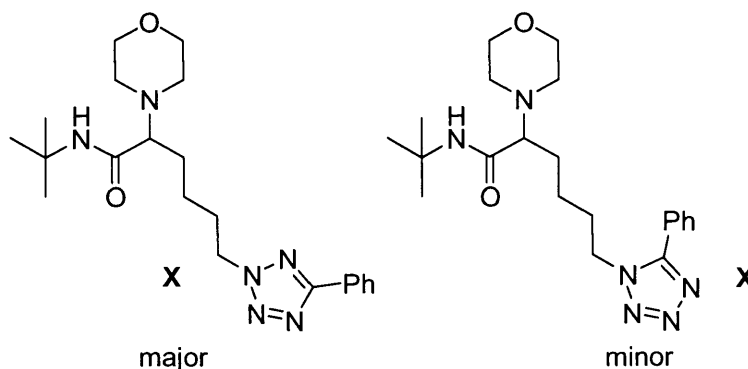
¹³C NMR (CDCl₃, 125 MHz) δ 23.06, 25.8, 28.46, 28.50, 47.6, 51.2, 60.13, 68.7, 123.8, 128.5, 129.1, 131.1, 154.1, 171.72.

HRMS - (CI (pos) methane) – calculated for C₂₀H₃₁N₄O: 371.25592, found 371.25524.

LRMS – (CI (pos) methane) 270 (100, M+H), 371 (88, M+H), 104 (64), 225 (41), 173 (27), 189 (25).

IR (thin film) ν max- 3335 (br, NH), 2964 (alkyl), 2888 (alkyl), 1663 (C=O amide), 1520, 1464, 1450 cm^{-1} .

N-tert-butyl-2-morpholino-6-(5-phenyl-2H-tetrazol-2-yl)hexanamide **260a** (major) and *N*-tert-butyl-2-morpholino-6-(5-phenyl-1H-tetrazol-1-yl)hexanamide **260b** (minor). (10:1 Mixture).



4-(Tetrahydro-2H-pyran-2-yl)morpholine **258** (342 mg, 2 mmol), 5-phenyl-1H-tetrazole (292 mg, 2 mmol), *p*TsOH (8 mg, 0.04 mmol) and then *tert*-butyl isocyanide (226 μl , 2 mmol) were added to anhydrous MeCN (2ml) and heated at reflux for 18 h under an atmosphere of N_2 . Excess solvent was removed under reduced pressure and the residue was purified by flash column chromatography (90:10:1 hexanes:EtOAc:TEA) to give *N*-tert-butyl-2-morpholino-6-(5-phenyl-2H-tetrazol-2-yl)hexanamide **260a** and *N*-tert-butyl-2-morpholino-6-(5-phenyl-1H-tetrazol-1-yl)hexanamide **260b** (10:1 Mixture) as a colourless oil (663 mg, 83%). R.f. = 0.44 (90:10:1 hexanes:EtOAc:TEA).

Major regioisomer ^1H NMR (CDCl_3) δ 1.16 (9H, s, t-Bu), 1.22-1.137 (2H, m, CH_2), 1.39-1.48 (2H, m, CHCH_2), 1.78-1.86 (2H, m, CH_2), 2.27-2.41 (4H, m, $\text{CH}_2\text{-N-CH}_2$), 2.55 (1H, t, J = 6.7 Hz, CH), 3.55 (4H, t, J = 4.8 Hz, $\text{CH}_2\text{-O-CH}_2$), 4.26 (2H, t, J = 7.2 Hz, N- CH_2), 6.62 (1H, bs, NH), 7.38-7.42 (3H, m, Ar), 7.49-7.54 (2H, m, Ar).

^{13}C NMR (CDCl_3 ,) δ 23.2, 27.2, 28.6, 29.3, 50.54, 52.7, 67.06, 69.5, 126.6, 127.4, 128.8, 130.1, 164.8, 171.2.

Minor regioisomer $^1\text{H NMR}$ (CDCl_3) δ 1.17 (9H, s, t-Bu), 1.22-1.1.37 (2H, m, CH_2), 1.50-1.59 (2H, m, CHCH_2), 1.88-2.00 (2H, m, CH_2), 2.27-2.41 (4H, m, $\text{CH}_2\text{-N-CH}_2$), 2.55 (1H, t, $J = 6.7$ Hz, CH), 3.55 (4H, t, $J = 4.8$ Hz, $\text{CH}_2\text{-O-CH}_2$), 4.50 (2H, t, $J = 7.0$ Hz, N- CH_2), 6.61 (1H, bs, NH), 7.28-7.37 (3H, m, Ar), 7.96-7.99 (2H, m, Ar).

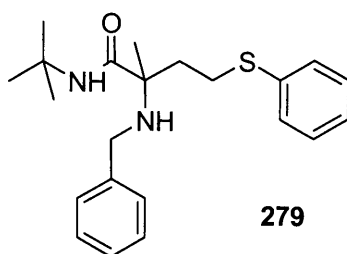
$^{13}\text{C NMR}$ (CDCl_3 ,) δ 23.4, 27.0, 28.6, 29.5, 47.7, 50.54, 67.06, 69.3, 123.8, 128.6, 129.2, 131.1, 154.2, 170.9.

HRMS - (FAB (pos)) – calculated for $\text{C}_{21}\text{H}_{33}\text{N}_2\text{O}_2$: 401.26649, found 401.26566.

LRMS – (FAB (pos)) 154 (100), 401 (62, M+H), 155 (24), 153 (15), 307 (14), 402 (13).

IR (thin film) ν max- 3320 (br, NH), 2963 (alkyl), 2952 (alkyl), 2863 (alkyl), 1663 (C=O amide), 1533, 1464, 1452 cm^{-1} .

N-tert-Butyl-2-methyl-2-phenylamino-4-phenylsulfanyl-butyramide 279.



4-Hydroxybutanone (172 μl , 2 mmol), benzylamine (219 μl , 2 mmol), thiophenol (205 μl , 2 mmol), *p*TsOH (4 mg, 0.02 mmol) and then *tert*-butyl isocyanide (226 μl , 2 mmol) were added to anhydrous MeCN (5ml) and heated at 45°C for 18 h under an atmosphere of N_2 . Excess solvent was removed under reduced pressure and the residue was purified by flash column chromatography (7:1 hexanes:EtOAc) to give *N-tert-Butyl-2-methyl-2-phenylamino-4-phenylsulfanyl-butyramide 279* (373 mg, 53 %) as a pale yellow oil R.f.= 0.32 (2:1 Hexanes:EtOAc) and 4-(Phenylthio)butan-2-one **280** as a colourless oil (137 mg, 38%).

¹H NMR (CDCl₃) δ 1.34 (9H, s, *t*-Bu), 1.37 (3H, s, CH₃), 1.97-2.04 (2H, m, CH₂), 2.14 (1H, s, NH), 2.91 (1H, ddd, *J* = 13.1, 9.9, 6.4 Hz, S-CH_ACH_B), 2.98 (1H, ddd, *J* = 13.1, 9.9, 6.7 Hz, S-CH_ACH_B), 3.53 (1H, d, *J* = 12.6 Hz, ArCH_AH_B), 3.68 (1H, d, *J* = 12.6 Hz, Ar-CH_AH_B), 7.13 (1H, tt, *J* = 6.2, 1.5 Hz, Ar), 7.25-7.39 (9H, m, Ar + NH).

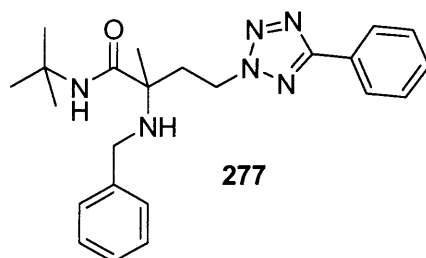
¹³C NMR (CDCl₃) δ 22.5, 28.6, 28.8, 38.6, 47.5, 50.4, 62.0, 126.1, 127.3, 127.9, 128.7, 129.0, 129.1, 129.2, 136.2, 140.0, 174.0.

HRMS - (EI) - calculated for C₂₂H₃₁N₂OS: 371.21571, found 371.21583.

LRMS - (EI) 371 (100 M+H), 372 (22), 393 (20, M+Na), 212 (8), 270 (6), 395 (5).

IR (thin film) ν max- 3345 br (NH), 3012 (aryl), 2998 (alkyl), 2887 (alkyl), 2952 (alkyl), 2913(alkyl), 1668 (C=O amide), 1583, 1480, 1439 cm⁻¹.

2-(Benzylamino)-*N*-tert-butyl-2-methyl-4-(5-phenyl-2*H*-tetrazol-2-yl)butanamide 277.



4-Hydroxybutanone (172 μl, 2 mmol), benzylamine (219 μl, 2 mmol), 5-phenyl-1*H*-tetrazole (292 mg, 2 mmol), *p*TsOH (4 mg, 0.02 mmol) and then *tert*-butyl isocyanide (226 μl, 2 mmol) were added to IPA (5ml) and heated at 45°C for 18 h under an atmosphere of N₂. Excess solvent was removed under reduced pressure and the residue was purified by flash column chromatography (4:1 hexanes:EtOAc) to give *N*-*tert*-Butyl-2-methyl-2-phenylamino-4-(5-phenyl-tetrazole-2-yl)-butyramide **277** as a colourless oil (211 mg, 26 %) R_f = 0.36 (2:1 Hexanes:EtOAc) and 4-(5-Phenyl-2*H*-tetrazol-2-yl)butan-2-one **278** as a colourless oil (234 mg, 54 %).

¹H NMR (CDCl₃) δ 1.38 (9H, s, *t*-Bu), 1.46 (3H, s, CH₃), 2.41 (1H, ddd, *J* = 14.2, 8.7, 6.2 Hz, CH_ACH_B), 2.50 (1H, ddd, *J* = 14.2, 8.5, 7.0 Hz, CH_ACH_B), 3.55 (1H, d, *J* =

12.7 Hz, Ar-CH_AH_B), 3.68 (1H, d, J= 12.7 Hz, Ar-CH_AH_B), 4.70 (1H, ddd, J= 13.8, 8.6, 6.2 Hz, N-CH_ACH_B), 4.87 (1H, ddd, J= 13.8, 8.7, 7.0 Hz, N-CH_ACH_B), 7.19-7.25 (5H, m, Ar), 7.41 (1H, bs, NH), 7.44-7.49 (3H, m, Ar), 8.06-8.14 (2H, m, Ar).

¹³C NMR (CDCl₃) δ 23.1, 28.7, 37.7, 47.5, 49.6, 50.7, 126.8, 127.3, 127.4, 127.7, 128.6, 128.9, 130.3, 139.5, 165.1, 173.4.

HRMS - (EI) – calculated for C₂₃H₃₁N₂O: 407.25593, found 407.25612.

LRMS – (EI) 407 (100 M+H), 360 (92), 338 (54), 429 (30), 317 (27), 261 (22).

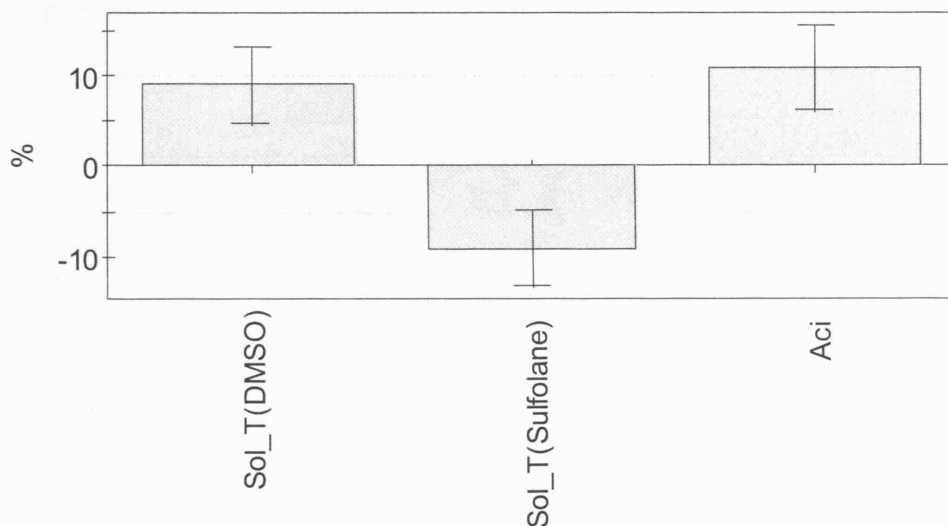
IR (thin film) ν max- 3370 br (NH), 3048 (aryl), 3007 (aryl), 2953 (alkyl), 2937 (alkyl), 2867 (alkyl), 1661 (C=O amide), 1516 (NH), 1451, 1362 cm⁻¹

Appendix.

4.1 Modde ® Plots for Design of Experiments #1 (Section 2.5) including ANOVA

tables.

Scaled & Centered Coefficients for 44hrs Side Product (Extended)



N=10

R²=0.892

R² Adj.=0.862

DF=7

Q²=0.781

RSD=5.5076

Conf. lev.=0.95

MODDE 7 - 26/07/2006 13:45:20

44hrs Side Product		Coeff. SC	Std. Err.	P	Conf. int(±)
Constant		28.5833	1.77756	8.74E-07	4.20332
Sol_T		DF = 1			
Sol_T(DMSO)		9.08333	1.77756	0.00138403	4.20332
Sol_T(Sulfolane)		-9.08333	1.77756	0.00138403	4.20332
Aci		11	1.94722	0.000775223	4.6045

N = 10

Q² =

0.781

Cond. no. =

1.2247

DF = 7

R² =

0.892

Y-miss =

0

R² Adj. =

0.862

RSD =

5.5076

Conf. lev. =

0.95

4.2 Modde ® Plots for Design of Experiments #2 (Section 2.6) including ANOVA tables.



N=20
DF=15

R2=0.922
Q2=0.844

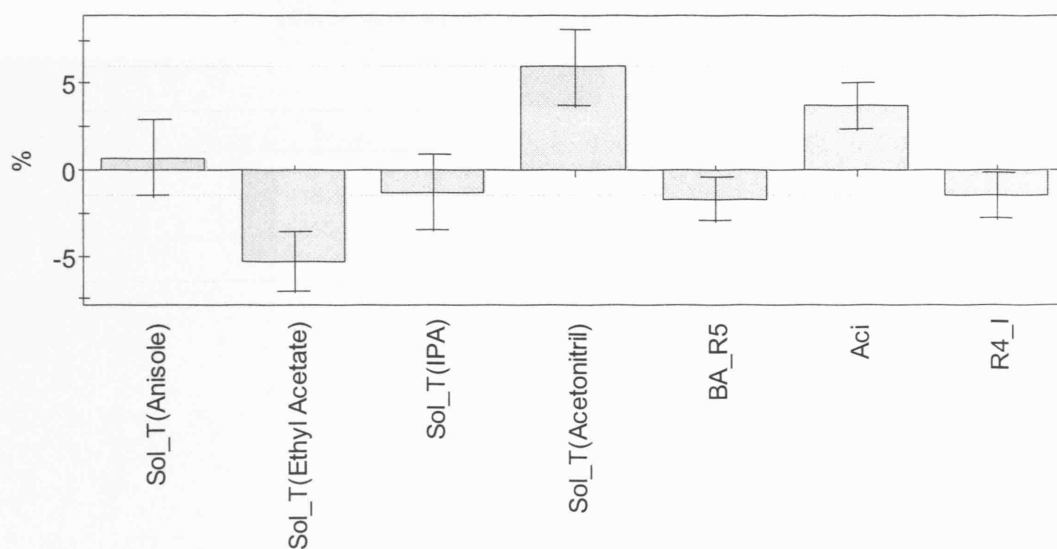
R2 Adj.=0.901
RSD=4.1493 Conf. lev.=0.95

MODDE 7 - 26/07/2006 11:01:30

24hrs Product	Coeff. SC	Std. Err.	P	Conf. int(±)
Constant	54.1875	0.970328	8.08962e-019	2.0682
Sol_T DF = 3				
Sol_T(Anisole)	-7.43751	1.75887	0.000729582	3.74892
Sol_T(Ethyl Acetate)	-15.1875	1.42041	2.05682e-008	3.02753
Sol_T(IPA)	13.5625	1.75887	1.35082e-006	3.74892
Sol_T(Acetonitril)	9.0625	1.75887	0.000118029	3.74892
Sol_C	-2.5	1.03732	0.0292445	2.21099

N = 20 Q2 = 0.844 Cond. no. = 2.3583
 DF = 15 R2 = 0.922 Y-miss = 0
 R2 Adj. = 0.901 RSD = 4.1493
 Conf. lev. = 0.95

Scaled & Centered Coefficients for 24hrs Side Product (Extended)



N=20
DF=13

R²=0.897
Q²=0.711

R² Adj.=0.849
RSD=2.3989 Conf. lev.=0.95

MODDE 7 - 26/07/2006 11:04:21

24hrs Side Product	Coeff. SC	Std. Err.	P	Conf. int(±)
Constant	23.0625	0.560996	3.76494e-015	1.21196

Sol_T	DF = 3			
Sol_T(Anisole)	0.687498	1.01689	0.51084	2.19686
Sol_T(Ethyl Acetate)	-5.3125	0.821213	2.1027e-005	1.77412
Sol_T(IPA)	-1.3125	1.01689	0.219291	2.19686
Sol_T(Acetonitril)	5.9375	1.01689	5.79067e-005	2.19686
BA_R5	-1.6875	0.59973	0.0146388	1.29564
Aci	3.6875	0.59973	3.49558e-005	1.29564
R4_I	-1.4375	0.59973	0.0322709	1.29564

N = 20 Q² = 0.711 Cond. no. = 2.3583
 DF = 13 R² = 0.897 Y-miss = 0
 R² Adj. = 0.849 RSD = 2.3989
 Conf. lev. = 0.95

Confounding structure

	Sol_T (Ethyl Acetate)	Sol_T (IPA)	Sol_T (Acetonitril)	Sol_C	BA_R5	Aci	R4_I	Temp
Sol_T(Ethyl Acetate)	1	0.422577	0.422577	0	0	0	0	0
Sol_T(IPA)	0.422577	1	0.5	0	0	0	0	0
Sol_T(Acetonitril)	0.422577	0.5	1	0	0	0	0	0
Sol_C	0	0	0	1	0	0	0	0
BA_R5	0	0	0	0	1	0	0	0
Aci	0	0	0	0	0	1	0	0
R4_I	0	0	0	0	0	0	1	0
Temp	0	0	0	0	0	0	0	1
Sol_T(Ethyl Acetate)*Sol_C	0	0	0	0	0	0	0	0
Sol_T(Ethyl Acetate)*BA_R5	0	0	0	0	0	0	0	0
Sol_T(Ethyl Acetate)*Aci	0	0	0	0	0	0	0	0
Sol_T(Ethyl Acetate)*R4_I	0	0	0	0	0	0	0	0
Sol_T(Ethyl Acetate)*Temp	0	0	0	0	0	0	0	0.258199
Sol_T(IPA)*Sol_C	0	0	0	0	0	0.707107	0	0
Sol_T(IPA)*BA_R5	0	0	0	0	0	0	0.707107	0
Sol_T(IPA)*Aci	0	0	0	0.707107	0	0	0	0
Sol_T(IPA)*R4_I	0	0	0	0	0.707107	0	0	0
Sol_T(IPA)*Temp	0	0	0	0	0	0	0	0
Sol_T(Acetonitril)*Sol_C	0	0	0	0	0	0.707107	0	0
Sol_T(Acetonitril)*BA_R5	0	0	0	0	0	0	0.707107	0
Sol_T(Acetonitril)*Aci	0	0	0	0.707107	0	0	0	0
Sol_T(Acetonitril)*R4_I	0	0	0	0	0.707107	0	0	0
Sol_T(Acetonitril)*Temp	0	0	0	0	0	0	0	0
Sol_C*BA_R5	0	0	0	0	0	0	0	0
Sol_C*Aci	0	0.707107	0.707107	0	0	0	0	0
Sol_C*R4_I	0	0	0	0	0	0	0	0
Sol_C*Temp	0	0	0	0	0	0	0	0
BA_R5*Aci	0	0	0	0	0	0	0	0
BA_R5*R4_I	0	0.707107	0.707107	0	0	0	0	0
BA_R5*Temp	0	0	0	0	0	0	0	0
Aci*R4_I	0	0	0	0	0	0	0	0
Aci*Temp	0	0	0	0	0	0	0	0
R4_I*Temp	0	0	0	0	0	0	0	0

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